VOLUME 23 · NUMBER 8 · MARCH 10 2005

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Adjuvant Endocrine Therapy for Premenopausal Women With Early Breast Cancer

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J Clin Oncol 23:1736-1750. © 2005 by American Society of Clinical Oncology

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Submitted November 15, 2004; accepted December 1, 2004.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2308-1736/$20.00

DOI: 10.1200/JCO.2005.11.050

INTRODUCTION

Approximately one third of newly diagnosed invasive breast cancers occur in women under 50 years of age.[1,2] It is likely that more women will be diagnosed with early-stage breast cancer at younger ages as a result of demographic and lifestyle changes, as well as progress in screening.[3,4]

While results from adjuvant endocrine therapy for postmenopausal women have recently improved through the use of aromatase inhibitors (AIs), this type of treatment continues to be a major clinical dilemma for premenopausal patients. Postmenopausal women with endocrine responsive disease are offered, at various times after surgery, with or without chemotherapy, a choice of endocrine therapies with either tamoxifen[5,6] or an AI. The latter has been tested in postmenopausal women either after surgery,[7] after 2 to 3 years of tamoxifen to complete standard duration of this drug,[8] or after 5 years of tamoxifen to further reduce the risk of relapse, especially for patients at high risk of recurrence (ie, node-positive disease).[9] The alternative drugs to tamoxifen, nonsteroidal and steroidal AIs, are particularly valuable when there are contraindications for tamoxifen (eg, history of thrombosis or embolism, or ocular diseases like retinal dysfunction). These considerations may apply for premenopausal patients as well, however, AIs are ineffective in the presence of premenopausal estrogen levels and information on their effect when given together with ovarian function suppression must await the completion of ongoing randomized clinical trials. Premenopausal women with endocrine responsive disease are usually offered tamoxifen with or without ovarian function suppression.[6] Adjuvant cytotoxic drugs are usually prescribed before endocrine therapy for many patients with endocrine responsive disease, especially if they are at high risk of relapse. The decision to use adjuvant cytotoxics in women with node-negative disease is controversial because despite the demonstrated treatment effects of chemotherapy in this age group, the effect might be partially or totally due to ovarian function suppression.[10]

There are several open questions that must be considered when reviewing the data on adjuvant endocrine therapies for premenopausal patients. These include the type and duration of ovarian function suppression as well as the best way for it to be combined with other types of endocrine therapies, including selective estrogen receptor modulators (SERMs), AIs, and selective estrogen receptor downregulators (SERDs). In fact, data on the essence and extent of endocrine effects of chemotherapy are scant and the specific roles of both ovarian function suppression and of chemotherapy remain uncertain.

The prognosis of breast cancer in young women is generally considered to be unfavorable. Between 1978 and 1993, the International Breast Cancer Study Group (IBCSG) treated 3,700 premenopausal and perimenopausal patients with various timing and duration of adjuvant cyclophosphamide,

methotrexate, and fluorouracil (CMF) without endocrine therapy. Three hundred fourteen of these women were younger than 35 years at randomization. The women less than 35 years with estrogen receptor (ER) –positive tumors had a significantly worse disease-free survival (DFS) than women less than 35 years with ER-negative disease. By contrast, among older premenopausal patients, the DFS was similar irrespective of ER status. Young premenopausal breast cancer patients treated with adjuvant CMF chemotherapy had higher risk of relapse and death than older premenopausal patients, especially if their tumors expressed estrogen receptors. Hence, the endocrine effects of chemotherapy alone are insufficient for the younger age group and these patients should strongly consider additional endocrine therapies (tamoxifen and/or ovarian ablation) if their tumors express ER.[11] Information from studies on 7,631 patients who were treated with chemotherapy alone in trials of three major US cooperative groups showed a similar interaction between the effect of very young age and steroid hormone receptor status of the primary tumor.[12] The development of more effective therapies for younger patients requires tailored treatment investigations and cannot rely on information predominantly contributed from older premenopausal women.

PROPER SELECTION OF ENDOCRINE RESPONSIVE DISEASE

For patients with operable breast cancer, the presence of increasing concentrations of steroid hormone receptors in the primary tumor is associated with an increased effectiveness of endocrine therapies. This association is observed in premenopausal patients treated with oophorectomy or tamoxifen.[13,14] The recognition of the increased role of endocrine therapy in properly selected patient groups has been recently described.[6] Determination of steroid hormone receptors in general depends upon several tumor- and patient-related factors: sampling method, tumor cellularity, organ site of the neoplastic tissue, sex, menopausal status, day of cycle (for premenopausal women), pregnancy and lactation, and drug administration (eg, steroid hormones).[15] The method of determination is crucial for identifying overexpression of ERs and progesterone receptors (PgRs). The ligand-binding assay, which was the first to be developed for commercial use, does not identify all endocrine responsive tumors, and currently an immunohistochemical method is recommended.[16] ER and PgR overexpression in $\geq$ 1% of the tumor cells is associated with some endocrine responsiveness of the tumor,[17,18] while absence of expression indicates endocrine nonresponsive disease. Recognition of the importance of the steroid hormone receptors evaluation will require current practices in many laboratories to change from reporting merely positive or negative receptor status (often adopting arbitrary cutoffs) in favor of more quantitative quality-controlled reporting of routine receptor determinations.[6] Molecular heterogeneity of ER and PgR has been linked to some cases of resistance and selection of cells with unresponsive mutants of receptors by endocrine therapies, such as tamoxifen.[19] Other biologic factors, such as expression of epithelial-growth factor receptor and c-*ErbB-2* (HER-2/*neu*), are associated with a poor response to endocrine therapy, especially with tamoxifen.[20] The mechanisms underlying this resistance are highly dependent upon the endocrine agent used.[21] For example, while tamoxifen resistance has been suggested for ER-positive tumors overexpressing HER-2, the combination of bilateral oophorectomy followed by tamoxifen was particularly effective compared with no adjuvant therapy for patients with this disease presentation.[22]

OVARIAN FUNCTION SUPPRESSION/ABLATION

Ovarian ablation was the first form of systemic treatment for advanced breast cancer.[23] Its use as an adjuvant therapy was suggested several decades later, and the first randomized trials of ovarian ablation in the adjuvant setting began in 1948. A meta-analysis of these early trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has unequivocally established that ovarian ablation as a single intervention, whether induced by surgery or radiotherapy, is associated with significant improvement in recurrence-free and overall survival (OS) among women less than 50 years of age at the time of treatment.[13] The EBCTCG presented their third 5-yearly systematic overview (meta-analysis) on ovarian ablation, with 15 years follow-up (Table 1). Data were included from 12 of the 13 studies that assessed ovarian ablation by irradiation or surgery (all begun before 1980), but not from the four studies that assessed ovarian suppression by drugs (begun after 1985). Menopausal status was not consistently defined in these trials; therefore, the main analyses were limited to women aged under 50 years (rather than premenopausal) when randomly assigned. ER was measured only in the more recently conducted trials that tested ovarian ablation plus cytotoxic chemotherapy versus the same chemotherapy alone. The benefit of ovarian ablation was smaller in these trials than in the trials that did not include chemotherapy, presumably due to endocrine effects of chemotherapy. Less than 60% of the patients included in the trials that contained chemotherapy were known to have ER-positive tumors. Women 50 years or older did not benefit from ovarian ablation. Indirect comparisons showed that the magnitude of the benefit derived from ovarian ablation in trials with no additional chemotherapy[13] was similar to that seen with adjuvant chemotherapy or tamoxifen in younger women.[14,24]

Table 1. Selected Results From the Early Breast Cancer Trialists' Collaborative Group Overview Analysis of Ovarian Ablation for Women Under 50 Years of Age[13]

	Recurrence-Free Survival				Overall Survival			
		Reduction in Odds				Reduction in Odds		
Patient Population	5-year %	%	SD	*P*	5-year %	%	SD	*P*
All with or without chemotherapy and irrespective of ER status, age within the < 50-year cohort, and nodal status (n = 2102)								
Ovarian ablation	45	18.5	5.5	.0007	52	18.4	5.7	.001
Control	39				46			
Without chemotherapy (n = 1169)								
Ovarian ablation	—	25	7	.0005	—	24	7	.0006
Control	—				—			
Without chemotherapy and node-negative (n = 473)								
Ovarian ablation	75	—	—	.01	77	—	—	.01
Control	67	—	—		71	—	—	
Without chemotherapy and node-positive (n = 696)								
Ovarian ablation	37	—	—	.0002	42	—	—	.0007
Control	24	—	—		29	—	—	
With chemotherapy (n = 933)								
Ovarian ablation	—	10	9	> .1	—	8	10	> .1
Control	—				—			
With chemotherapy and ER-positive only (n = 550)								
Ovarian ablation	—	13	11	> .1	—	17	13	> .1
Control	—				—			

NOTE. Em dashes represent information not available in the published report.[13]
Abbreviation: ER, estrogen receptor.

Surgical Oophorectomy

Surgical oophorectomy was the first form of ovarian ablation tested. It causes an immediate and permanent drop in ovarian steroid production. Current methods of laparoscopic surgery have dramatically reduced operative morbidity and mortality. Oophorectomy is assumed also to reduce the risk of ovarian cancer in women who are carriers of predisposition genes.[25,26]

Radiation-Induced Ovarian Ablation

Radiation-induced ovarian ablation is performed using several treatment algorithms, ranging from 4.5 Gy in one fraction to 10 to 20 Gy over five to six fractions. Radiation-induced ovarian ablation is a safe and simple outpatient approach, but it may be incomplete or significantly delayed in some women.[25] Biochemical verification of ovarian function cessation is thus required.

Gonadotropin Hormone-Releasing Hormone Analogs

Time-limited ovarian function suppression can be achieved with luteinizing hormone- or gonadotropin hormone-releasing hormone (LHRH or GnRH) agonists. LHRH agonists have been used during the past 25 years and are safe and reversible with no permanent ovarian dysfunction and with a side effect profile related to menopausal estrogen deprivation symptoms.[25,27] The response rate with goserelin was similar to that of oophorectomy in patients with metastatic breast cancer.[27] There is no convincing comparison among the three forms of ovarian function suppression/ablation, and the current preferred use of GnRH analogs is due to their reversible action. Hence, duration of treatment is potentially most critical in decision making.[28]

Chemotherapy

Cytotoxic chemotherapy represents a fourth form of ovarian ablation because of its capacity to cause temporary or permanent ovarian dysfunction in premenopausal women. Chemotherapy has been the mainstay of adjuvant therapy for premenopausal women with node-positive disease since the first trials of combination chemotherapy demonstrated significant benefits, especially for the younger cohort.[29,30] The use of chemotherapy was not considered a reasonable option for the minimal- or low-risk group of patients, despite available information on the efficacy of adjuvant chemotherapy, mainly in premenopausal patients.[31] How much of this benefit is due to the endocrine effects of chemotherapy is still a matter for research.[32,33]

It has been argued that cytotoxic chemotherapy is beneficial for premenopausal women with breast cancer because it causes premature menopause. Studies to date have not resolved the issue, although evidence appears to support the hypothesis of a dual mechanism of action of chemotherapy in this patient population: direct

cytotoxicity and ovarian suppression resulting from chemotherapy-induced ovarian failure.[34] There is ample preclinical and clinical evidence to support a direct cytotoxic mechanism of action. The evidence supporting the gonadotoxic mechanism of action of chemotherapy is indirect but compelling biologically. Chemotherapy, particularly with alkylators such as cyclophosphamide, can cause ovarian fibrosis with a concomitant loss of function. Furthermore, amenorrhea and premature menopause are well known side effects of adjuvant chemotherapy for breast cancer.[35] Although the meta-analysis demonstrating a highly clinically significant benefit of ovarian ablation mainly compared the roles of radiation-induced and surgery-induced castration versus control not involving ovarian ablation, there is no scientific reason why chemotherapy-induced ovarian failure would not confer benefit, particularly in patients with hormone receptor–positive disease.[13] However, because there are no mature randomized phase III data that directly test this question and the results of subset analyses of completed phase III studies using amenorrhea as a surrogate marker of ovarian failure are inconsistent,[36] the extent of benefit rendered by chemocastration is unknown.

The risk of chemotherapy-related amenorrhea is directly related to age at time of treatment and varies with type, dose, and duration of chemotherapy. In general, less than 50% of women under 40 years of age will be rendered postmenopausal by standard adjuvant chemotherapy regimens, whereas the majority of women aged 40 years or older will become permanently menopausal. Rates of permanent amenorrhea have been reported for several commonly used adjuvant chemotherapy regimens. They range from about 40% after four cycles of doxorubicin and cyclophosphamide (AC) with or without four cycles of paclitaxel to nearly 70% for six cycles of oral CMF, with a lower likelihood of becoming amenorrheic with six cycles of intravenous CMF compared with six cycles of oral CMF.[25,37-40] Table 2 describes amenorrhea rates associated with various regimens used in the adjuvant setting.[40-43] Figure 1 shows the probability of menopause according to the patient's age during the first year after diagnosis based on a mathematical model.[44] Results from clinical trials comparing chemotherapy with endocrine therapy and to their combination should thus be assessed according to patient age, as the proportion of patients who benefit from chemotherapy via endocrine mechanisms is age dependent.

Table 2. Rates of Chemotherapy-Induced Amenorrhea[40]

Study	Adjuvant Chemotherapy	Incidence of Amenorrhea
Goldhirsch et al[12]	Classic CMF	< 35 years: 4% temporary; 8% permanent; 88% no amenorrhea
		≥ 35 years: 7% temporary; 59% permanent; 34% no amenorrhea
Bines et al[37]	AC	34%
Nabholtz et al[41]	FAC	32.8%
	TAC	51.4%
Hortobagyi et al[42]	Doxorubicin-based	59%
Levine et al[43]	CEF	51%

Abbreviations: CMF, cyclophosphamide, methotrexate, fluorouracil; AC, doxorubicin, cyclophosphamide; FAC, fluorouracil, doxorubicin, cyclophosphamide; TAC. docetaxel, doxorubicin, cyclophosphamide; CEF, cyclophosphamide, epirubicin, fluorouracil.

Efficacy of Ovarian Function Suppression/Ablation

Adjuvant studies of ovarian ablation during the last 50 years have focused largely on three major questions. The usefulness of ovarian ablation versus no postoperative therapy was tested first. The increasing use of chemotherapy and the recognition that some of its effect could be related to ovarian function suppression led to randomized studies of adjuvant chemotherapy versus ovarian ablation with or without tamoxifen. Finally, several recent trials have examined the possibility that ovarian ablation provides additional benefit for young women after adjuvant chemotherapy.[25,45]

Clinical trials conducted to investigate the role of ovarian function suppression/ablation alone are summarized in Table 3. The Zoladex Early Breast Cancer Research Association[46,50] and IBCSG VIII[10] trials compared goserelin (3.6 mg every 28 days for 2 years) versus CMF (six 28-day courses of cyclophosphamide, methotrexate and fluorouracil) irrespective of ER status for node-positive and node-negative cohorts, respectively. Both studies demonstrated a significant interaction between treatment and ER status; goserelin and CMF gave equivalent results for the ER-positive cohort, but goserelin was inferior to CMF for the ER-negative population. The Scottish trial also demonstrated an interaction, with ablation being

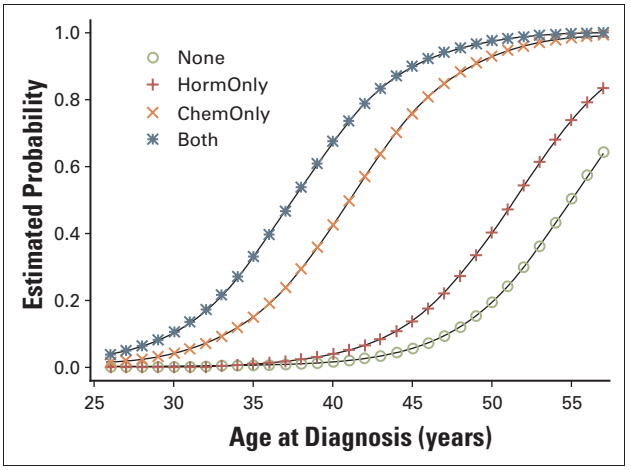

Fig 1. Probability of menopause during the first year after diagnosis (based on a model).[44]

Table 3. Trials of Ovarian Function Suppression/Ablation Compared With Chemotherapy That Does Not Include Tamoxifen

Study	Author	Treatment	Patients	Results
ZEBRA (N = 1,640)	Kaufmann et al[46]	CMF × 6 (n = 823) G × 2 years (n = 817)	N+; ER+/−	CMF = G for DFS for ER+: [HR = 1.05; 95% CI, 0.88 to 1.24; *P* = .6] CMF > G for DFS for ER−
IBCSG VIII (N = 1,063)	IBCSG[10]	CMF × 6 (n = 360) G × 24 months (n = 346) CMF × 6 → G × 18 months (n = 357)	N−; ER+/−	CMF = G for DFS for ER+: [HR = 0.97; 95% CI, 0.66 to 1.42; *P* = 0.86] CMF→G = G for DFS for ER+: [HR = 0.84; 95% CI, 0.56 to 1.26; *P* = .40] CMF→G = CMF for DFS for ER+: [HR = 0.80; 95% CI, 0.54 to 1.19; *P* = .26]
Scottish (N = 332)	Thomson et al[47]	CMF × 6 to 8 OA (oophorectomy)	N+	No difference overall: [HR = 1.12; 95 CI, 0.76 to 1.63] OA > CMF for OS for ER ≥ 20 fmols/mg CMF > OA for ER < 20 fmols/mg
Scandinavian (N = 732)	Ejlertsen et al[48]	CMF × 9 OA (RT)	N+; ER+	No difference
TABLE (N = 600)	Schmid et al[49]	CMF × 6 Leuprorelin × 2 years	N+; ER+	No difference

NOTE. <, worse than; >, better than; =, equal to.
Abbreviations: HR, hazard ratio; ZEBRA, Zoladex Early Breast Cancer Research Association; CMF, cyclophosphamide, methotrexate, fluorouracil; N−, node negative; G, goserelin; ER, estrogen receptor; DFS, disease-free survival; IBCSG, International Breast Cancer Study Group; N+, node positive; OA, ovarian ablation; OS, overall survival; RT, radiation therapy; TABLE, Takeda Adjuvant Breast cancer study with Leuprorelin Acetate.

superior to CMF for patients with tumors having ER concentrations ≥ 20 fmol/mg cytosol protein, but inferior to CMF for lower values of ER.[47] Retrospective determination of ER by immunohistochemistry confirmed the importance of tailoring treatment according to ER status and identified an ER-poor cohort for whom endocrine manipulation is inappropriate.[51] The Scandinavian[48] and the Takeda Adjuvant Breast Cancer Study with Leuprorelin Acetate[49] trials, which restricted enrollment to patients with ER-positive tumors, also showed no difference between CMF and ovarian ablation/suppression.

Because in the early 1990s, the benefit of tamoxifen for premenopausal women was uncertain, the trials reviewed above did not include tamoxifen in the study design. Thus, the relative effects of tamoxifen, ovarian function suppression, and chemotherapy for premenopausal women with endocrine responsive disease have yet to be defined. This is unfortunate, as tamoxifen has become a mainstay of management for these patients.

TAMOXIFEN

The EBCTCG updated its overview analysis of tamoxifen trials in 1995 and results were available in the 1998 report.[14] Among women with ER-positive tumors, when the data were analyzed by age and duration of tamoxifen therapy, the trials in which tamoxifen was given for 5 years to women younger than 50 years revealed proportional risk reductions of 45% in recurrence and 32% in mortality. Unfortunately, EBCTCG analyses of tamoxifen conducted in 1990 and reported in 1992 showed only a modest effect of tamoxifen on recurrence and no effect on mortality for women below the age of 50 years.[52] This analysis of the tamoxifen effect was conducted across the board without considering the role of ER status of the primary and combining results of trials with various durations of tamoxifen and with and without chemotherapy.[53] The negative results had a chilling effect both on the use of tamoxifen and on the inclusion of tamoxifen in clinical trials for premenopausal patients. In 1990, however, the analyses of trials without chemotherapy, which also tended to test longer durations of tamoxifen, suggested a large benefit for tamoxifen in this age group.[53] This benefit was revealed in the 1998 report, which tailored the analysis to focus on women with ER-positive tumors who were enrolled in trials that tested 5 years of tamoxifen.

Table 4 summarizes many of the clinical trials that evaluated tamoxifen in the adjuvant setting. Results consistently support its use as endocrine therapy for both premenopausal and postmenopausal women, especially for steroid hormone receptor positive disease.

The Nolvadex Adjuvant Trial Organization (NATO),[54] National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14,[55,56] and Scottish trials[57-59] assessed tamoxifen alone against no adjuvant therapy or a placebo group. Both the NSABP B-14 and the Scottish trials rerandomized patients who remained disease-free after 5 years of tamoxifen to either stop tamoxifen or continue for an additional 5 years.[56,58] Neither trial demonstrated a benefit from continuing tamoxifen but an increased risk of endometrial cancer was noted in the Scottish trial.[59] Thus, 5 years is the recommended duration of tamoxifen treatment.

Tamoxifen was compared with chemotherapy in the The Italian Breast Cancer Adjuvant Study Group

Table 4. Trials of Tamoxifen

Study	Author	Treatment	Patients	Results
NATO (N = 605)	NATO[54]	Tam 20 mg × 2 years (n = 300) No treatment (n = 305)	N−, premenopausal and postmenopausal	Tam > No treatment for DFS and OS
NSABP B-14 (N = 2,644)	Fisher et al[55]	Tam 20 mg × 5 years Placebo	N−, ≤ 49 and ≥50 years old, ER+	Tam > Placebo for DFS: overall, 83% versus 77%, $P < .00001$; ≤ 49 years old, $P = .0005$; ≥ 50 years old, $P = .0008$). Recurrence rate reduced by 44% in ≤ 49 years old (all sites) No difference in OS ($P = .3$)
NSABP B-14, Tam beyond 5 years (N = 1,172)	Fisher et al[56]	Tam × 5 more years (n = 593) Placebo (n = 579)	N−, ≤ 49 and ≥50 years old, ER+ (after 5 years of Tam in NSABP B-14)	No difference in DFS and OS at 4 years At 7 years, Tam < Placebo for DFS ($P = .03$), RFS ($P = .13$), OS ($P = .07$)
Scottish trial (N = 1,323)	Stewart[57]	Tam 20 mg × 5 years after surgery (n = 667) Tam after relapse (n = 656)	N−, premenopausal and postmenopausal	Tam > Nil for DFS; overall ($P = .0001$); premenopausal (n = 214, $P = .018$); postmenopausal (n = 533, $P = .0026$) Tam > Nil for RFS ($P = .029$) NS for OS ($P = .07$) Beneficial effect (maintained through 15 years) of adjuvant tamoxifen on the % of total survival ($P = .006$), systemic relapse ($P = .007$) and death from breast cancer ($P = .002$).
Scottish trial, Tam beyond 5 years (N = 342)	Stewart et al[58,59]	Tam continued until relapse and death (n = 173) No further therapy (n = 169)	N−, (after 5 years of Tam in the Scottish trial)	No difference in outcome; increased risk of endometrial cancer if Tam > 5 years ($P = .064$)
GROCTA (N = 504)	Boccardo et al[60]	Tam × 5 years CMF × 6 → E × 4 CMF × 6 → E × 4 + Tam × 5 years	N+, ER+, premenopausal (n = 237)	In premenopausal patients: no difference for DFS and OS between Tam and CT Tam: excess of locoregional relapses (hyperestrogenic effect of Tam in premenopausal patients)
GABG (N = 331)	Kaufmann et al[61]	CMF IV Tam × 2 years	1-3 positive nodes, < 50 years old, ER+	CMF > Tam for DFS and OS
IBCSG 13-93 (N = 1,246)	Colleoni et al[62]	AC × 4 → CMF × 3 → Tam × 5 years AC × 4 → CMF × 3 → No treatment	N+, pre-perimenopausal	Tam > No treatment for DFS: [HR = 0.76; 95% CI, 0.63 to 0.91; $P = .004$] ER+: [HR = 0.61; 95% CI, 0.48 to 0.79; $P = .0001$] ER low: [HR = 0.85; 95% CI, 0.62 to 1.16; $P = .29$] ER absent: [HR = 1.95; 95% CI, 0.95 to 4.00; $P = .07$]
DBCG 82B (N = 634)	Andersson et al[63]	CMF × 9 (n = 314) CMF × 9 + Tam 30 mg × 1 year (n = 320)	Stage II-III, pre-perimenopausal, 40% ER+, 12% ER−, 48% ER unknown	No difference in RFS ($P = .81$) No difference in OS ($P = .73$)
NSABP B-09 (N = 1,891)	Fisher et al[64]	PF PF + Tam × 2 years	N+, premenopausal and postmenopausal, ER+/−	Significant prolongation of DFS ($P = .002$), no prolongation of OS. Benefit for patients ≥ 50 years with ≥ 4 N+, for whom 66% greater chance of remaining disease-free if PFT was received ($P < .001$) and significant survival benefit ($P = .02$). Significant improvement in DFS from PFT in ER or PgR ≥ 10 fmol ($P = .01$ and $P = .009$, respectively) No significant benefit in DFS or OS in patients ≤ 49 years old; survival adversely affected by Tam in ≤ 49 years old, PgR 0-9 fmol ($P = .007$)

(continued on next page)

Table 4. Trials of Tamoxifen (continued)

Study	Author	Treatment	Patients	Results
NSABP B-20 (N = 2,306)	Fisher et al[65]	Tam (n = 771) MF + Tam (n = 767) CMF + Tam (n = 768)	N−, ≤ 49 and ≥50 years old, ER+	CMF + Tam and MF + Tam > Tam for DFS and OS (especially for ≤ 49 years old)
ECOG (N = 553)	Tormey et al[66]	CMF × 12 months (n = 188) CMFP × 12 months (n = 183) CMFPT × 12 months (n = 182)	N+, premenopausal, ER+/−	Overall, no difference for TTR and OS CMFPT > CMF for TTR in > 3 N+ (P = .07) and in ER− with > 3 N+ (P = .03). CMFPT > CMF for OS in ER− with > 3 N+ (P = .02)
NCCTG (N = 400)	Ingle et al[67]	CFP × 10 CFP × 10 + Tam 20 mg × 1 year	N+, premenopausal, ER+/−	CFPT > CFP for RFS (P = .06) No difference for OS (P = .21)
GUN (N = 433)	De Placido et al[68]	Tam 30 mg × 2 years (n = 206) Controls (n = 227) 308 premenopausal N− and postmenopausal N− or N+: Tam 30 mg × 2 years No further therapy 125 premenopausal N+: CMF × 9 + Tam × 2 years (n = 60) CMF × 9 (n = 65)	Stage I, II, or III (T3a), premenopausal and postmenopausal, ER+/−	Tam > No therapy for RFS and OS CMF + Tam = CMF for RFS and OS

NOTE. <, worse than; >, better than; =, equal to.
Abbreviations: NATO, Nolvadex Adjuvant Trial Organization; Tam, tamoxifen; N−, node negative; DFS, disease-free survival; OS, overall survival; NSABP, National Surgical Breast and Bowel Project; ER, estrogen receptor; RFS, relapse free survival; GROCTA, Gruppo di Ricerca in Oncologia Clinica e Terapie Associate; CMF, cyclophosphamide, methotrexate, fluorouracil; E, epirubicin; CT, chemotherapy; GABG, Gynecological Adjuvant Breast Group; IV, intravenous; IBCSG, International Breast Cancer Study Group; AC, doxorubicin, cyclophosphamide; HR, hazard ratio; DBCG, Danish Breast Cancer Cooperative Group; PF, L-phenylalanine mustard and fluorouracil; PFT, L-phenylalanine mustard and fluorouracil plus tamoxifen; N+, node positive; PgR, progesterone receptor; MF, methotrexate, fluorouracil; ECOG, Eastern Cooperative Oncology Group; CMFP, CMF + prednisone; CMFPT, CMFP + Tam; TTR, time to relapse; NCCTG, North Central Cancer Treatment Group; CFP, cyclophosphamide, fluorouracil, prednisone; GUN, Gruppo Universitario Napoletano.

(GROCTA)[60] and the Gynecological Adjuvant Breast Group (GABG)[61] studies for premenopausal women with ER-positive tumors. The chemotherapy group did better than the tamoxifen alone group in both trials, although statistical significance was only reached in the GABG study.

Whether tamoxifen should routinely be recommended after chemotherapy in premenopausal women with endocrine responsive disease is unclear. Although the most recent overview analysis showed a risk reduction of 40% for recurrence and 39% for mortality for chemotherapy plus tamoxifen versus chemotherapy alone among premenopausal women with ER-positive disease, very few patients were included in the analysis.[14] In 1993, the IBCSG initiated trial 13-93 for premenopausal and perimenopausal patients with lymph-node–positive disease to examine the role of adjuvant treatment using chemotherapy, or the sequential combination of chemotherapy and tamoxifen. A total of 1,246 patients were to receive chemotherapy (AC × four cycles followed by immediate or delayed classical CMF × three cycles) alone or followed by tamoxifen (20 mg daily) for 5 years. DFS was significantly improved for the tamoxifen group compared with the no tamoxifen group, especially for patients with ER-positive tumors (Table 4). The tamoxifen benefit was much less and not statistically significant for patients with tumors expressing low levels of ER, and a detrimental effect of tamoxifen was observed for patients with no expression of ER in the tumor (so-called ER-absent; Table 4).[62] An additional trial, conducted by the National Cancer Institute of Canada Clinical Trials Group, randomly assigned over 800 premenopausal women to tamoxifen or no tamoxifen following AC, CMF, or CEF (cyclophosphamide, epirubicin, and fluorouracil), and is currently in follow-up.

Tamoxifen is associated with a variety of side effects including increased risk for endometrial cancer and thromboembolic disorders.[69] Investigations of bone mineral density in patients treated with prolonged tamoxifen have reported a possible decrease of density in premenopausal women.[70] By contrast, the Scottish Trial has reported a decrease in the risk of death from myocardial infarction for patients treated with tamoxifen.[57]

OVARIAN FUNCTION SUPPRESSION/ABLATION PLUS TAMOXIFEN WITH OR WITHOUT CHEMOTHERAPY

Besides being as effective as surgical castration in inducing ovarian function suppression, LHRH agonists can also suppress the tamoxifen-induced stimulation of ovarian function. This represented the rationale for combining LHRH analogs and tamoxifen in premenopausal women. In a meta-analysis of four clinical trials randomly assigning 506 premenopausal women with advanced breast cancer to LHRH agonist alone or to the combined treatment of LHRH agonist plus tamoxifen, after a median follow-up of 6.8 years there was a significant survival benefit (P = .02) and progression-free survival benefit (P = .0003) in favor of the combined treatment. The

overall response rate was significantly higher on combined endocrine treatment ($P = .03$).[71]

Several studies in the adjuvant setting have shown that the combination of ovarian function suppression/ablation plus tamoxifen is safe and at least as effective as chemotherapy for premenopausal patients with ER-positive disease (Table 5). The Austrian Breast Cancer Study Group Trial 5[72] in 1,034 patients demonstrated a significant benefit in terms of relapse-free survival for patients who received goserelin for 3 years plus tamoxifen for 5 years compared with those who received CMF for six courses. The GROCTA 02 study showed that results for ovarian ablation (surgery, radiation or goserelin for 2 years) plus tamoxifen for 5 years were similar to those of six courses of CMF.[73] Two small French trials[74,75] compared complete hormonal blockade to six courses of an anthracycline-containing regimen for premenopausal women with node-positive, ER-positive disease. One study compared combined hormonotherapy with either surgical or radiotherapeutic castration plus tamoxifen 30 mg for 2 years versus six cycles of fluorouracil, adriamycin, and cyclophosphamide every 3 weeks. At a median follow-up of 7 years, the endocrine therapy arm demonstrated statistically nonsignificant higher DFS percentage (82.8% *v* 55%) and OS percentage (84% *v* 74%) compared with chemotherapy alone.[74] The French Adjuvant Study Group 06 study compared triptorelin (3.75 mg intramuscular every month) plus tamoxifen (30 mg/d) for 3 years versus six cycles of FEC 50 (fluorouracil, epirubicin, cyclophosphamide) every 3 weeks in women with one to three positive axillary lymph nodes. At 54 months of median follow-up, both DFS (91.7% *v* 80.9%) and OS (97% *v* 92.9%) were nonsignificantly higher for the endocrine therapy regimen.[75]

The Zoladex in Premenopausal Patients (ZIPP) trial was a collaboration among four study groups that used a 2 × 2 design to study goserelin for 2 years, tamoxifen for 2 years, their combination, and no endocrine therapy. The study permitted the use of elective chemotherapy in

Table 5. Trials of Ovarian Function Suppression/Ablation That Include Tamoxifen

Study	Author	Treatment	Patients	Results
ABCSG (N = 1,034)	Jakesz et al[72]	CMF × 6 G × 3 years + Tam × 5 years	Node+/−, ER+	CMF < G + Tam for DFS: [HR = 1.40; 95% CI, 1.06 to 1.87; $P = .017$]
GROCTA 02 (N = 244)	Boccardo et al[73]	OA (surgery, RT, or G × 2 years) + Tam 30 mg × 5 years (n = 124) CMF × 6 (n = 120)	Node+/−, ER+	G + Tam = CMF: [HR = 0.94; 95% CI, 0.60 to 1.47; $P = 0.80$]
France (N = 162)	Roché et al[74]	FAC × 6 OA (surgery or RT) + Tam 30 mg × 2 years	Node+, ER+	No difference (see text)
FASG 06 (N = 333)	Roché et al[75]	Tam 30 mg + triptorelin × 3 years (n = 164) FEC × 6 (n = 169)	Node+, ER+	No difference (see text)
ZIPP (N = 2,631)	Rutqvist[76]	G × 2 years Tam × 2 years G × 2 years+ Tam × 2 years No further treatment	Node+/−, ER+/−	G > no G: [HR = 0.77; 95% CI, 0.66 to 0.89; $P < .001$]
INT-0101 (N = 1,504)	Davidson et al[77]	CAF CAF+ G × 5 years CAF+ G + Tam × 5 years	Node+, ER+	CAF + G = CAF: [HR = 0.93; 95% CI, 0.76 to 1.14; $P = .25$] CAF + G + Tam > CAF + G: [HR = 0.73; 95% CI, 0.59 to 0.90; $P < .01$]
Vietnamese (N = 709)	Love et al[78]	OA (surgery) + Tam × 5 years Observation	Node+/−	OA + Tam > Observation for DFS and OS
France (N = 926)	Arriagada et al[79]	Chemotherapy (any) Chemotherapy (any) + OA (RT/medical)	Node+/−	No difference
Mam-1 GOCSI (N = 466)	Bianco et al[80]	CMF A→CMF CMF→G + Tam × 2 years A→CMF→G + Tam × 2 years	Node+, ER+/−	G + Tam arms > chemotherapy alone: [HR = 0.71; 95% CI, NR; $P = .04$]
IBCSG 11-93 (N = 174)	IBCSG[81]	AC × 4 + OA (G, surgery or RT) + Tam 20 mg × 5 years OA (G, surgery or RT) + Tam 20 mg × 5 years	Node+, ER+	No difference (see text)

NOTE. <, worse than; >, better than; =, equal to.
Abbreviations: HR, hazard ratio; ABCSG, Austrian Breast and Colorectal Cancer Study Group; CMF, cyclophosphamide, methotrexate, fluorouracil; G, goserelin; ER, estrogen receptor; Tam, tamoxifen; DFS, disease-free survival; GROCTA, Gruppo di Ricerca in Oncologia Clinica e Terapie Associate; OA, ovarian ablation; RT, radiation therapy; FAC, fluorouracil, adriamycin, cyclophosphamide; FASG, French Adjuvant Study Group; FEC, fluorouracil, epirubicin, cyclophosphamide; ZIPP, Zoladex in Premenopausal Patients; INT, North American Breast Cancer Intergroup Trial; CAF, cyclophosphamide, doxorubicin, fluorouracil; OS, overall survival; GOCSI, Gruppo Oncologico Central Sud Isole; A, adriamycin; NR, not reported; IBCSG, International Breast Cancer Study Group; AC, doxorubicin, cyclophosphamide.

selected patients and investigators could elect to use tamoxifen or not and randomize only for the goserelin question. The goserelin-containing groups had significantly better DFS and a trend toward better OS compared with no goserelin, especially for ER-positive disease. Goserelin was effective, although apparently to a somewhat lesser degree, for patients who also received tamoxifen and for those who also received chemotherapy.[76]

In the Intergroup Trial 0101, all patients (premenopausal, node-positive, ER-positive) received six courses of cyclophosphamide, doxorubicin, and fluorouracil chemotherapy and either no endocrine therapy, goserelin for 5 years, or goserelin plus tamoxifen for 5 years. The addition of goserelin alone did not significantly improve outcome, but the combination of goserelin and tamoxifen significantly improved DFS compared with the other regimens.[77]

In a trial conducted in Vietnam, over 700 premenopausal women with early-stage breast cancer were randomly assigned to oophorectomy plus 5 years of tamoxifen either at the time of mastectomy or at the time of relapse. Preliminary results suggest that adjuvant combined endocrine therapy improved DFS and OS compared with initial observation, but only for women with steroid-receptor–positive tumors.[78]

Although chemotherapy and ovarian function suppression are both effective adjuvant therapies for patients with early-stage breast cancer, little is known about the efficacy of their sequential combination. In the IBCSG Trial VIII,[10] 1,063 pre- and perimenopausal patients with lymph-node–negative breast cancer were randomly assigned to receive goserelin for 24 months, six courses of classical CMF, or six courses of classical CMF followed by 18 months of goserelin. After a median follow-up of 7 years, patients with ER-negative tumors benefited from CMF. By contrast, patients with ER-positive tumors had similar results with CMF alone and goserelin alone, and a statistically nonsignificant better outcome with the combined treatment, primarily because of the results among younger women. The combination regimen induced a more profound and longer duration of amenorrhea in younger women compared with the single modality regimens, which may have contributed to its slightly better effect for these patients.

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 (IBCSG trial 11-93), which recruited 174 premenopausal women with lymph-node–positive disease, who were randomly assigned to receive either four cycles of AC plus ovarian function suppression (goserelin, bilateral oophorectomy, or ovarian irradiation) plus 5 years of tamoxifen (20 mg/d) or endocrine therapy (ovarian function suppression plus tamoxifen) alone.[81] 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 DFS was 87% for the group that received AC and 88% for the endocrine therapy alone group. The small number of patients enrolled in IBCSG trial 11-93 does not permit a definitive answer to the question about whether adding chemotherapy to ovarian function suppression plus tamoxifen improves outcome compared with the combined endocrine therapy alone. This question remains clinically relevant and is being investigated in an ongoing randomized trial (the Premenopausal Endocrine Responsive Chemotherapy [PERCHE] study).

The clinical trial results discussed above and presented in Table 5 demonstrate that ovarian function suppression/ablation plus tamoxifen is at least as effective as chemotherapy for premenopausal patients with ER-positive disease. A current clinical controversy relates to the management of patients with endocrine responsive disease who remain premenopausal (continue to menstruate) following completion of their chemotherapy. These patients would routinely receive tamoxifen after chemotherapy. The Suppression of Ovarian Function Trial (SOFT) is currently investigating whether adding ovarian function suppression/ablation together with tamoxifen following chemotherapy improves results compared with tamoxifen alone following chemotherapy.

OTHER ENDOCRINE THERAPIES

AIs

Estrogens have a crucial role in breast cancer. Estradiol is biosynthesized from androgens by the enzyme complex called aromatase. Inhibition of aromatase is an important approach for reducing growth stimulatory effects of estrogens in estrogen-dependent breast cancer. Both steroidal and nonsteroidal AIs have shown clinical efficacy for the treatment of postmenopausal breast cancer.[82]

The issue of using AIs in premenopausal women, either alone or with tamoxifen, was raised despite the theoretical argument against their efficacy in the presence of ovarian derived estrogens. YM511, a nonsteroidal selective AI, has been evaluated as a single agent in premenopausal women. It was hypothesized that in this situation, site-specific suppression of estrogens in breast carcinomas, without systemic effects, may lead to a downregulation of tumor proliferation. However, despite increased plasma levels of androstenedione and testosterone and suppressed mean plasma estrone levels, some plasma estradiol levels were abnormally high and others abnormally low, and YM511 did not demonstrate antiproliferative effects in hormone-sensitive breast carcinomas, while ovarian production remained high.[83]

Treatment with AIs in premenopausal women together with GnRH analogs is obviously potentially effective. The combined use of goserelin and anastrozole as second-line endocrine therapy following progression on goserelin and tamoxifen produced significant clinical responses of worthwhile duration, with demonstrable endocrine changes, in premenopausal women (n = 16) with advanced breast cancer.[84]

Unfortunately, no trial has yet been conducted in the adjuvant setting to investigate the role of AIs plus ovarian function suppression compared with tamoxifen plus ovarian function suppression or with tamoxifen alone, either with or without chemotherapy, in premenopausal women with endocrine-responsive disease. These questions are being addressed by a suite of three ongoing tailored clinical trials coordinated by the IBCSG on behalf of the Breast International Group and the North American Breast Cancer Intergroup.[85,86] The three trials (called SOFT, TEXT [Tamoxifen and Exemestane Trial], and PERCHE [STP]) are designed for two patient populations (Table 6). SOFT compares tamoxifen alone versus ovarian function suppression (by either the GnRH analog triptorelin or bilateral oophorectomy or ovarian irradiation) plus tamoxifen versus ovarian function suppression plus exemestane (a steroidal AI) for patients with steroid hormone receptor–positive tumors who remain premenopausal after adjuvant chemotherapy or for whom tamoxifen alone is considered a reasonable treatment option. Thus, SOFT addresses the current dilemma concerning whether or not ovarian function suppression should be initiated for patients who continue to menstruate following adjuvant chemotherapy. The complementary TEXT trial compares the GnRH analog triptorelin plus tamoxifen versus triptorelin plus exemestane for patients who receive the GnRH analog with or without chemotherapy from the start of their adjuvant therapy program. SOFT and TEXT both provide comparisons of tamoxifen with exemestane in the adjuvant 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 AI, may be sufficient to achieve excellent outcomes without chemotherapy, especially for patients at low risk of recurrent disease.[81] This question is being investigated in the 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 hormone receptor–positive tumors who receive ovarian function suppression from the start of their adjuvant therapy program (Table 6). TEXT and PERCHE are available for the same patient population and a woman may be enrolled in both studies—PERCHE to determine whether chemotherapy will be given or not, and TEXT to determine whether tamoxifen or exemestane will be used.

OTHER SERMs AND SERDs

No data on other SERMs (eg, raloxifene, toremifene, and idoxifen) or SERDs (eg, fulvestrant) are available in premenopausal women.

Table 6. Ongoing Clinical Trials* Testing Endocrine Therapies and Endocrine Effects of Chemotherapy for Premenopausal Patients with Endocrine Responsive Breast Cancer†

Patient Population	Title	Design
Patients who remain premenopausal after adjuvant chemotherapy or for whom tamoxifen alone is considered a reasonable treatment option	SOFT—Suppression of Ovarian Function Trial (IBCSG 24-02, BIG 2-02)	Premenopausal estradiol 2 weeks to 6 months following completion of chemotherapy or within 12 weeks of primary surgery for patients who do not receive chemotherapy, randomize to: • Tamoxifen × 5 years • OFS + tamoxifen × 5 years • OFS + exemestane × 5 years
Patients who receive GnRH analog with or without chemotherapy from the start of their adjuvant therapy program	TEXT—Tamoxifen and Exemestane Trial (IBCSG 25-02, BIG 3-02)	Premenopausal estradiol within 12 weeks of primary surgery, randomize to: • Triptorelin (+/− CT) + tamoxifen × 5 years • Triptorelin (+/− CT) + exemestane × 5 years
Patients who receive ovarian function suppression from the start of their adjuvant therapy program.	PERCHE—Premenopausal Endocrine Responsive Chemotherapy trial (IBCSG 26-02, BIG 4-02)	Premenopausal estradiol within 12 weeks of primary surgery, randomize to: • OFS + tam/exe × 5 years • OFS + CT + tam/exe × 5 years

NOTE. Patients may enrol in PERCHE alone, TEXT alone, or both PERCHE and TEXT. For more information about the STP (SOFT, TEXT, PERCHE) studies, e-mail: STP@IBCSG.org.
Abbreviations: IBCSG, International Breast Cancer Study Group; BIG, Breast International Group; OFS, ovarian function suppression (by either the GnRH analog triptorelin for five years or bilateral oophorectomy or ovarian irradiation); GnRH, gonadotropin-releasing hormone; CT, chemotherapy (in TEXT use of CT is according to investigator/patient choice or by random assignment in PERCHE); tam/exe, tamoxifen or exemestane (in PERCHE use of tamoxifen or exemestane is according to investigator/patient choice or by random assignment in TEXT).
*Coordinated by the IBCSG on behalf of BIG and the North American Breast Cancer Intergroup.[85,86]
†Premenopausal status determined by estradiol levels and endocrine responsive disease determined by steroid hormone receptor positivity (estrogen receptor or progesterone receptor positive—recommended method is immunohistochemistry ≥ 10% of cells stained positive).

COMBINING BIOLOGICAL COMPOUNDS WITH ENDOCRINE AGENTS

Most traditional cancer treatment regimens are generally nonselective, inducing cytotoxicity in normal as well as in malignant cells. In developing novel anticancer agents, the goal is to target specific molecular lesions within tumor cells (eg, HER-2), leading to improved cure rates and reducing cytotoxicity in normal cells.[87] Advances in the understanding of tumor pathobiology and molecular biology have allowed the development of targeted therapies.[88] The human epidermal growth factor receptor family of receptors is considered an important therapeutic target, and various types of small molecules, including monoclonal antibodies, protein tyrosine kinase inhibitors, and vaccines are in development as potential therapies for metastatic breast cancer.[88,89] Studies of these novel agents in the adjuvant setting must be designed to assess their activity separately for patients with endocrine responsive disease—who will receive endocrine therapy—and for patients with endocrine nonresponsive disease. The type of endocrine therapy (eg, tamoxifen with or without GnRH analog, or AI) and the endocrine effects of menopausal status may also influence the magnitude of treatment effect obtainable from a targeted therapy (eg, trastuzumab). Tailored treatment evaluation of the new biologic compounds is required to properly integrate them into current treatment practice.

GnRH Analogs and Tamoxifen in c-ErbB2 Overexpressing Breast Cancer

One concern associated with prescribing tamoxifen alone to a premenopausal patient is that the presence of factors such as HER-2 overexpression may reduce its efficacy.[90] However, in a study conducted by Love et al[22] on 282 ER-positive breast cancer patients randomly assigned to adjuvant oophorectomy and tamoxifen versus observation, the magnitude of the benefit in favor of the combined endocrine therapy was greater for the HER-2/*neu*-positive cohort than for the HER-2/*neu*-negative group (hazard ratios for DFS were 0.37 and 0.48 [interaction $P = .18$]; hazard ratios for OS were 0.26 and 0.68 [interaction $P = .07$]). Thus, HER-2/*neu* overexpression does not adversely influence, and may favorably influence, response to adjuvant oophorectomy and tamoxifen treatment in patients with ER-positive tumors.[22]

SPECIAL ISSUES

Acceptance of Endocrine Therapies, Especially for the Very Young

Despite the encouraging efficacy data and the marked differences in the impact on quality of life of the various adjuvant therapy choices, many clinicians do not routinely offer premenopausal women the option to receive GnRH analogs. An ongoing treatment preference survey of 200 healthy (without cancer) premenopausal women ages 25 to 49 years currently reports an overwhelming preference for goserelin compared with chemotherapy ($P < .0001$). Overall, women viewed the written description of the side-effect profile of goserelin as more acceptable, valued the chance to retain their fertility, and preferred the method of administration with the endocrine option.[91] The side effects of ovarian function suppression actually experienced by breast cancer patients should not be underestimated. A study in 345 patients demonstrated significantly more menopausal symptoms and significantly worse quality of life, including sexual dysfunction, among women randomly assigned to receive tamoxifen plus ovarian suppression/ablation compared with tamoxifen alone.[92]

A substudy in the ZIPP trial compared the effect of adjuvant endocrine therapies with and without chemotherapy on physical symptoms, anxiety, and depressive symptoms in premenopausal women. Patients treated with CMF reported higher levels of physical symptoms than did patients who did not receive CMF. After completion of the 2 years of goserelin, the side effects diminished in patients who had not received CMF, whereas patients treated with CMF reported ongoing problems at the 3-year follow-up.[93] Further assessments of the influence of endocrine therapies with or without chemotherapy on the quality of life of premenopausal women are required and are included as a component of the ongoing STP trials.

Endocrine Therapy and Pregnancy

Preservation of ovarian function by ovarian suppression during chemotherapy. Long-term survival is likely when breast cancer is diagnosed at an early stage, especially after adjuvant therapy. Temporary or permanent menopause is a consequence that specifically affects young women diagnosed with breast cancer and treated with adjuvant chemotherapy. In addition, premature ovarian failure in women without breast cancer has been associated with increased age-specific mortality rate.[3,94]

Infertility represents one of the main sequelae of cytotoxic therapy given for various malignant diseases. Because dividing cells are more sensitive to cytotoxic effects than are cells at rest, it has been hypothesized that inhibition of the pituitary-gonadal axis may facilitate the preservation of future gonadal function. Several studies in patients receiving chemotherapy for nonbreast malignancies or nonmalignant autoimmune disorders have been conducted and demonstrate that administering GnRH analog before and during chemotherapy suppresses the pituitary-gonadal axis and may preserve ovarian function following chemotherapy.[95-97] Investigators from the Southwest Oncology Group (SWOG) have designed a phase III trial of GnRH-analog administration during

chemotherapy to reduce ovarian failure following standard adjuvant chemotherapy in early-stage, hormone receptor–negative breast cancer (SWOG 0230). Premenopausal women with confirmed diagnosis of operable stage I, II, and IIIA invasive breast cancer, with ER- and PgR-negative tumors, aged between 18 and 50 years, are eligible. The trial is currently open to enrollment.

Ovarian tissue preservation versus other forms of assisted reproductive technology treatments. Whereas sperm banking is commonly performed, female gametes are not so amenable to cryopreservation. One alternative includes postponing cancer treatment to enable ovulation induction and oocyte aspiration. Whenever possible, retrieved oocytes should be fertilized in vitro before cryopreservation. Frozen embryos could serve to produce pregnancies if ovarian failure occurs. Donor sperm can be offered to single patients, as frozen-thawed unfertilized oocytes yield poor pregnancy rates. Ovarian cortex cryopreservation should still be considered an experimental technology as no pregnancies have been obtained in humans. Therefore, ovarian cortex banking should be used only for young girls, adolescents, and when in-vitro fertilization (IVF) is contraindicated. Reattachment of ovarian vasculature could prevent ischemic follicular loss and enable ovarian transplantation in the future. This procedure is currently under investigation in animals. At the present time, we recommend urgent IVF in most patients requesting fertility preservation. Ovarian cryopreservation might be viewed as a promising alternative when emergency IVF is not possible.[98] All attempts to preserve fertility, however, need to be considered with extreme caution because methods have not been tested in the context of breast cancer and their influence on the natural history of the disease is unknown.

Safety of endocrine therapies for grown children of mothers who conceived after tamoxifen or other endocrine agents. Tamoxifen is as effective as clomiphene for induction of ovulation and patients are usually advised to use proper contraceptive methods during treatment. Pregnancy during or immediately after treatment with tamoxifen might cause some birth defects including genital tract and facial malformations. These effects are rare but should be taken into account when counseling young women on this issue. No data are available on late effects of tamoxifen on young women whose mothers had tamoxifen exposure before or during pregnancy.

CONCLUSIONS AND FUTURE DIRECTIONS

Premenopausal patients with ER-positive tumors represent a distinct population for which tailored treatment is needed. Endocrine therapy is mandatory in this population. Despite the numerous advances in adjuvant hormonal therapy for premenopausal women, several issues require further research. These include: (1) the importance of amenorrhea as a determinant for premenopausal women with early-stage breast cancer; (2) the optimal duration of ovarian function suppression with LHRH analogs; (3) the value of ovarian function suppression/ablation after chemotherapy, particularly for women who remain premenopausal after adjuvant chemotherapy; (4) the role of combination endocrine therapies in premenopausal women (ovarian function suppression plus tamoxifen or AIs); (5) the definitive role and best use of AIs in premenopausal patients; (6) careful delineation of the long-term side effects of AIs; (7) the worth of chemotherapy for patients at low risk for recurrence who receive optimal endocrine therapy; (8) the combination of new targeted therapies and endocrine treatments; and (9) specific issues related to child bearing and endocrine therapies.

Acknowledgment

We thank the patients, physicians, nurses, and data managers who participate in the International Breast Cancer Study Group trials. We also acknowledge the initial support provided by the Ludwig Institute for Cancer Research and the Cancer League of Ticino, and the continuing support for central coordination, data management, and statistics provided by the Swiss Group for Clinical Cancer Research (SAKK), Frontier Science and Technology Research Foundation, The Cancer Council Australia, Australian New Zealand Breast Cancer Trials Group (ANZ BCTG), United States National Cancer Institute (CA-75362), and Swedish Cancer Society. We also acknowledge support for the Cape Town participants from the Cancer Association of South Africa and for the St. Gallen participants from the Foundation for Clinical Cancer Research of Eastern Switzerland.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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