Adjuvant endocrine therapy for perimenopausal women with early breast cancer

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Abstract

Adjuvant treatment with aromatase inhibitors (AIs) improves outcomes in postmenopausal women with hormone-sensitive early breast cancer compared with tamoxifen. However, AIs should not be used in premenopausal women because they can paradoxically increase estrogen secretion and may therefore stimulate tumor progression. In perimenopausal women undergoing treatment for breast cancer, it can be difficult to determine true menopausal status because adjuvant chemotherapy, tamoxifen, and gonadotropin-releasing hormone analogues can induce transient (or permanent) ovarian suppression. How can one determine whether these women are truly postmenopausal and therefore candidates for AI therapy? A panel of experts in the field of endocrine therapy in breast cancer met in Dubrovnik, Croatia, on October 23, 2006, to discuss this clinical dilemma. This report summarizes the conclusions and recommendations that arose from this discussion.

Introduction

About one third of all early invasive breast cancer cases are diagnosed in women aged <50 years, a large proportion of whom are perimenopausal.1–3 Following surgery, the majority of patients receive adjuvant cytotoxic chemotherapy (CT)4 that can lead to partial or complete suppression of ovarian function.5 Although the incidence of CT-induced amenorrhea varies by treatment protocol, it is more frequent in patients aged >40 years (Table 1).3

Adjuvant CT is often followed by adjuvant endocrine therapy. In premenopausal patients, tamoxifen— with or without ovarian function suppression (OFS)—is the current standard of care for patients with hormone receptor–positive disease following surgery/radiation and CT.4 OFS is achieved by ovariectomy, radiation, or more frequently by the application of luteinizing hormone–releasing hormone (LHRH) agonists. However, it is unclear what the optimal adjuvant endocrine treatment is for premenopausal women with endocrine-responsive breast cancer. The use of aromatase inhibitors (AIs) in premenopausal women as up-front, sequential, or extended treatment is becoming a standard of care based on results from randomized controlled trials demonstrating improved clinical outcomes of such treatment strategies compared with 5-year tamoxifen alone.4,6 In postmenopausal women, AIs deplete estrogen levels by inhibiting or inactivating the enzyme aromatase in peripheral tissues and tumors.7,8 In women with residual ovarian function, AI-induced suppression of estrogen synthesis can trigger a reflex increase in gonadotropins, which in
Table 1
Reported incidence of amenorrhea with various chemotherapeutic regimens.

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<th>CT Regimen</th>
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CMF—cyclophosphamide/methotrexate/fluorouracil; CT—chemotherapy; FEC—fluorouracil/epirubicin/cyclophosphamide.

Data from Ref. 3.

Some oncologists have expanded the use of AIs to include patients aged >40 years with no signs of ovarian function in terms of regular menses, patients with CT-induced amenorrhea, or—on an empiric basis—in combination with ovarian suppression using LHRH agonists. Recent reports have documented a return of ovarian function and menstruation in some women with apparent CT-induced amenorrhea, even if hormonal levels seemed to confirm suppression of ovarian function. Adding gonadotropin-releasing analogues to adjuvant CT regimens have similarly been shown in retrospective studies to protect long-term ovarian function in some early breast cancer patients, although there is controversy surrounding this issue. The potential protective effects of LHRH agonists on ovarian function will partly be addressed by ongoing breast cancer trials, such as the Prevention of Early Menopause Study (POEMS), which evaluates ovarian protection in hormone-receptor-negative patients. However, additional prospective clinical studies examining ovarian protection as an endpoint are needed in hormone-responsive early breast cancer. A recent meta-analysis demonstrated that addition of an LHRH agonist to chemotherapy regimens does not decrease the efficacy of cytotoxic treatment in premenopausal patients with hormone receptor–positive breast cancer. The same meta-analysis also demonstrated that LHRH agonists and certain chemotherapy regimens are equally efficacious, so the option exists for patients to receive LHRH agonist monotherapy instead of chemotherapy. Also, according to a study conducted by Fallowfield et al. in healthy premenopausal or perimenopausal patients, a significant preference for LHRH agonist therapy over chemotherapy was expressed by the majority of patients (p < 0.00001).

In the following case studies, we describe the most common situations for using an AI as adjuvant endocrine therapy in younger primary breast cancer patients who may still have ovarian function.

Case studies

Case 1: premenopausal, estrogen receptor (ER)–positive, node-positive, HER2/neu-negative patient with contraindication to tamoxifen

A 40-year-old woman presented with stage IIA (T2 N0 M0) breast cancer. Patient had regular menstrual cycles, and levels of gonadotropins and estradiol were in the normal range for premenopausal women. Subsequent tumorectomy revealed a 3-cm grade 2 invasive ductal carcinoma. Sentinel lymph node biopsy was positive, and axillary dissection revealed involvement in 3 of 15 nodes. Pathology showed 80% ER-positive cells, with no cells positive for progesterone receptor (PgR). Immunohistochemical analysis was negative for HER2/neu.

The patient refused CT. Because of the relatively high risk of relapse, combined endocrine therapy with an LHRH agonist and an AI was recommended. Patient agreed to combination therapy with goserelin and exemestane. During treatment, gonadotropins and estradiol were monitored at 3-month intervals and were consistently within the postmenopausal range.

The patient completed 2 years of combined endocrine therapy with no evidence of progression or recurrence. She has experienced grade 2 hot flushes and night sweats and mild memory loss. Ongoing treatment options include continued combination therapy with goserelin and exemestane, definitive ovarian ablation and continued AI, or definitive ovarian ablation and a switch to tamoxifen. It was recommended that the patient continue the current treatment protocol to complete up to 5 years of endocrine therapy.

Case 2: premenopausal, ER-positive, node-positive, HER2/neu-negative patient who refused CT

A 40-year-old woman presented with stage IIA (T2 N0 M0) breast cancer. Patient had regular menstrual cycles, and levels of gonadotropins and estradiol were in the normal range for premenopausal women. Subsequent tumorectomy revealed a 3-cm grade 2 invasive ductal carcinoma. Sentinel lymph node biopsy was positive, and axillary dissection revealed involvement in 3 of 15 nodes. Pathology showed 80% ER-positive cells, with no cells positive for progesterone receptor (PgR). Immunohistochemical analysis was negative for HER2/neu.

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Case 3: perimenopausal, ER-positive, node-positive, HER2/neu-positive patient with contraindication to tamoxifen

A 45-year-old premenopausal woman presented to the physician. The patient had monthly menstruation at presentation, but hormone levels were not measured to confirm perimenopausal classification. Chest radiograph, echography of the liver, and bone scans indicated stage IIb (T2 N1 M0) bifocal invasive ductal carcinoma with ductal carcinoma in situ (DCIS). A mastectomy, axillary node dissection, and immediate reconstruction were performed on
June 27, 2006. Pathology confirmed 2 invasive carcinomas (3.7 and 0.2 cm) lying in a 6.5-cm zone of DCIS, with macrometastasis (breakthrough of the node capsule) in 1 of 24 dissected nodes. Pathology established the hormone receptor–positive status of tumors (immunoreactive scores were 10 for ER and 4 for PgR); fluorescence in situ hybridization was positive for HER2/neu.

The patient received 3 cycles of adjuvant 5-fluorouracil (500 mg/m²), epirubicin (100 mg/m²), and cyclophosphamide (500 mg/m²) (FE100C), followed by 3 cycles of docetaxel 100 mg/m². Because the patient had a history of hereditary spherocytosis with frequent hemolytic crises for which she had previously undergone a splenectomy, prophylactic granulocyte colony-stimulating factor was prescribed during docetaxel treatment. Approximately 2 months after completion of CT, patient received radiotherapy to the chest wall and internal mammary lymph nodes (50 Gy in 25 fractions). Patient was amenorrheic after the third cycle of FE100C. Laboratory values following completion of docetaxel were in the postmenopausal range (FSH = 60.8 IU/L; estradiol = 10 ng/L).

Because of the high risk of recurrence and HER2/neu-positive tumor status, it was recommended that the patient undergo adjuvant treatment with the monoclonal antibody trastuzumab and endocrine therapy. Because tamoxifen is associated with an increased risk of thrombosis and the patient had a history of spherocytosis and hemolytic crisis, endocrine therapy with an AI was considered preferable to tamoxifen. It was recommended that AI therapy be combined with chemical or surgical ovarian ablation to ensure an ongoing postmenopausal state.

The relative risks of available treatment options were discussed with the patient, who decided on definitive surgical ovarian ablation and 5 years adjuvant letrozole 2.5 mg daily.

**Endocrine therapy for early breast cancer in premenopausal and perimenopausal women**

**Determination of ovarian function**

Regular menses occur in healthy women during their reproductive years and are a sign of cyclic ovarian function. About 3–5% of women experience premature ovarian failure (POF), defined as cessation of ovarian function in women aged <40 years. In women aged 40–44 years, estrogen and progesterone secretion by the ovaries may be reduced. The duration of the transition period from premenopause to postmenopause varies considerably among women.14 This interim period is defined as perimenopause or menopausal transition. Efforts have been made to develop methods to predict the time of menopause onset (ie, last menstrual bleeding). The criteria for defining perimenopause differs extensively from trial to trial (Table 2). Because gonadotropin levels generally increase during perimenopause, with concomitant decreases in serum estradiol levels,2 most investigators have used FSH and estradiol measurements to help determine that menopause has transpired.5,14–17 However, these and other predictive means are not completely reliable. Because hormone levels vary widely, a retrospective determination of the time of menopause can usually be made if vaginal bleeding does not occur for >12 months in women aged >40 years. In most assays conducted during postmenopause, levels of estradiol are low and FSH measurements are consistently above 40 IU/mL.18 Other studies have demonstrated the utility of serum analyses of antimüllerian hormone and inhibin B, as well as functional ovarian ultrasonography measurements, to assess ovarian reserve in premenopausal breast cancer patients.19,20 Thus, combining these tests with measurements of hormone and gonadotropin levels may provide a more accurate estimation of ovarian function in premenopausal and perimenopausal patients. However, these methods cannot indisputably prove that permanent cessation of ovarian function has occurred; therefore, repeated determination of estradiol and FSH levels while monitoring the clinical signs of ovarian function is the best method of assessing menopausal status. Future prospective studies focused on safe application of AIs to this group of patients should help confirm this information.

**Patients of reproductive age**

Metastatic breast cancer patients with regular ovarian cycles who are treated with combinations of LHRH analogues and tamoxifen experience superior results compared with those treated with tamoxifen alone.21 In premenopausal patients, AIs are contraindicated because they do not decrease estrogen levels when administered alone. However, estrogen levels can be lowered by combining AIs with LHRH analogues or other methods of OFS, with concomitant monitoring of serum estrogen and gonadotropin levels.22,23 The potential benefit of combination therapy was first documented in studies with an LHRH agonist and the second-generation AI formestane, which showed significantly greater suppression of circulating estrogens in premenopausal patients than was reported with the LHRH agonist alone.22,24,25 More recently, a study in healthy premenopausal volunteers found that administration of the third-generation AI exemestane with the LHRH agonist triptorelin resulted in significantly greater suppression of plasma estradiol and estrone levels than those observed after triptorelin and placebo administration.26 A small phase II trial in premenopausal patients with ER–positive metastatic breast cancer found that the combination of anastrozole and goserelin produced a clinical benefit in 72% of patients.27 However, currently there are few data from randomized controlled trials that investigate the efficacy of such regimens. Ongoing trials include Suppression of Ovarian Function Trial (SOFT), International Breast Cancer Study Group (IBCSG 24-02), the Tamoxifen and Exemestane Trial (TEXT, IBCSG, 25–02),2,6 and the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSD-12), from which bone mineral density substudy data were recently published.28

If treatment with LHRH analogues in combination with AIs is selected (eg, for patients with contraindications against tamoxifen), ovarian suppression is achieved by initial application of the LHRH analogue. Suppression generally occurs within 7–14 days, but its occurrence should be assessed by measurement of gonadotropin and estradiol levels, which are low or undetectable depending on the detection method used. Subsequently, AIs can be coadministered, although additional estradiol measurements should be performed to confirm that ovarian suppression has persisted.

Women of reproductive age who have experienced POF may be candidates for adjuvant endocrine therapies that include an AI. In these cases, POF should be confirmed by repeated determination that estradiol and FSH measurements are at postmenopausal levels. No prospective trials have been performed yet to demonstrate how frequently hormone measurements are necessary. For clinical practice determination of estradiol and FSH levels every 2 to 3 months for the first year of AI treatment, and every 6 months thereafter, appears to be sufficient. The duration of amenorrhea before AI application is also of importance and may influence the frequency of hormone measurements in individual patients.

**Perimenopausal patients**

Some premenopausal patients have clinical signs of ovarian function (ie, irregular menstrual periods), intermittent high FSH measurements, and low estradiol levels during their menopausal transition stage. Because ovarian endocrine stimulation is associated with AI treatment in women with residual ovarian function, these women should not receive an AI alone, although they might
still benefit from AI monotherapy at later periods of adjuvant treatment. Although these perimenopausal patients may be treated with an AI plus OFS or ovarian ablation, generally they are started on tamoxifen therapy. In subsequent years, a switch to an AI after ovarian function has ceased emerges as a potential therapeutic option. However, this rationale for a switch to AI therapy is based on indirect evidence from trials performed in postmenopausal patients. It should be remembered that tamoxifen might influence hormonal levels, such as increasing estradiol levels in premenopausal women (an effect that is not detrimental to the efficacy of

Table 2
Clinical criteria for defining postmenopause.

<table>
<thead>
<tr>
<th>Agency/Trial</th>
<th>Criteria (1 or more)</th>
<th>Reference</th>
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<tbody>
<tr>
<td>ABCSG 8/ARNO 95</td>
<td>• Last menses ≥12 months before trial entry • Postmenopausal levels of LH and FSH • Prior bilateral oophorectomy</td>
<td>31</td>
</tr>
<tr>
<td>ATAC</td>
<td>• Prior bilateral oophorectomy • Aged ≥60 y or 45–59 y with an intact uterus and amenorrheic for ≥12 months • FSH concentrations in the postmenopausal range if amenorrheic for &lt;12 months (including patients who had undergone a hysterectomy and those who had received hormone replacement therapy or who had been rendered amenorrheic by CT)</td>
<td>32</td>
</tr>
<tr>
<td>IES</td>
<td>• Aged ≥55 y with amenorrhea for &gt;2 y • Amenorrhea for &gt;1 y at the time of diagnosis</td>
<td>33</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>Regardless of HRT or hysterectomy • Surgical bilateral oophorectomy and any age • Radiation castration and amenorrheic for ≥3 months and any age • Not postmenopausal at the start of adjuvant CT and completed ≥6 cycles of CMF or ≥4 cycles AC and aged ≥45 y and FSH/LH/E2 at postmenopausal levels No HRT • Hysterectomy and aged &lt;55 y and FSH/LH/E2 at postmenopausal levels before CT • Hysterectomy and aged ≥55 y No HRT and no hysterectomy • Amenorrhea &gt;1 y and aged &lt;50 y • Amenorrhea ≥6 months and aged ≥50 y HRT (regardless of hysterectomy); • HRT stopped for ≥1 months and aged &lt;55 y and FSH/LH/E2 at postmenopausal levels before chemotherapy • HRT stopped for ≥1 months and aged ≥55 y</td>
<td>34</td>
</tr>
<tr>
<td>ITA</td>
<td>• Missing regular menses ≥1 y • Aged ≥50 y and with hysterectomy • Confirmed amenorrhea following CT • When unclear, FSH and E2 measured</td>
<td>35</td>
</tr>
<tr>
<td>MA.17</td>
<td>• Prior bilateral oophorectomy • Premenopausal and aged ≤50 y at the start of tamoxifen therapy but became amenorrheic during CT or treatment with tamoxifen, or if they had postmenopausal levels of FSH and LH</td>
<td>36</td>
</tr>
<tr>
<td>NCCN</td>
<td>• Prior bilateral oophorectomy • Aged ≥60 y • Aged &lt;60 y and amenorrheic for ≥12 months in the absence of CT, tamoxifen, toremifene, or ovarian suppression and FSH and E2 in the postmenopausal range • If taking tamoxifen or toremifene, and aged &lt;60 y, then FSH and plasma E2 level in postmenopausal ranges It is not possible to assign menopausal status to women who are receiving an LHRH agonist or antagonist. In women who are premenopausal at the time of adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status.</td>
<td>4</td>
</tr>
<tr>
<td>PENN-5</td>
<td>• ≥12 months of amenorrhea</td>
<td>37</td>
</tr>
<tr>
<td>STRAW</td>
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</tr>
<tr>
<td>SWAN</td>
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<td>37</td>
</tr>
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ABCSG 8/ARNO 95 = Austrian Breast and Colorectal Cancer Study Group trial 8 and Arimidex/Nolvadex 95 combined analysis; AC = doxorubicin/cyclophosphamide; ATAC = Arimidex, Tamoxifen, Alone or in Combination trial; BIG 1-98 = Breast International Group 1-98; CMF = cyclophosphamide/methotrexate/fluorouracil; CT = chemotherapy; E2 = estradiol; FSH = follicle-stimulating hormone; HRT = hormone replacement therapy; IES = Intergroup Exemestane Study; ITA = Italian Tamoxifen Anastrozole trial; LH = luteinizing hormone; MA.17 = National Cancer Institute of Canada Clinical Trials Group MA.17 study; NCCN = National Comprehensive Cancer Network; PENN-5 = Penn Ovarian Aging Study; STRAW = Stages of Reproductive Aging Workshop; SWAN = Study of Women’s Health Across the Nation.

* Received within 3 months of randomization.
tamoxifen treatment). Ovarian function termination has to be determined reliably based on menses cessation, clinical signs of postmenopause, and measurements of estradiol and FSH levels. When the diagnosis of postmenopause has been established and therapy is continued with an AI, repeated measurements of estradiol and FSH levels should be performed on an individualized basis, taking into consideration age and clinical signs of ovarian function resumption.

Patients aged >40 years are at high risk for entering into definitive postmenopause following administration of cytotoxic CT.15 However, CT-induced ovarian failure should not necessarily be considered permanent in patients who were premenopausal or perimenopausal at diagnosis. A growing number of reports indicate that CT-induced amenorrhea is reversible and that ovarian function may be stimulated by treatment with an AI.14,16 Indeed, switching to an AI may induce a return of ovarian function and menstruation, even after extended periods of amenorrhea during tamoxifen treatment.15

Patients with contraindications to tamoxifen

Some premenopausal or perimenopausal patients may have contraindications to tamoxifen, such as thromboembolic disease25,30. In these patients can be treated after CT with OFS instead of tamoxifen. However, controversy exists regarding the efficacy of OFS following CT administration. This perceived lack of effect may be due to the proportion of premenopausal patients, particularly those aged >40 years, who are amenorrheic because of CT. For patients with no signs of ovarian function, AI alone may be the treatment of choice. It should be remembered that some patients, especially those aged <40 years, may resume ovarian function after CT. Thus, repeated measurements of estradiol and FSH levels should be performed even if there is no menstrual bleeding. If ovarian function is suspected at the beginning of treatment with an AI or occurs while the patient is on AI treatment, then OFS is mandatory.

Patients with moderate to high risk for recurrence

Oncologists strive to offer the most effective adjuvant endocrine treatment to patients with moderate to high risk for disease recurrence. Although there are no current data to support this course of treatment, AIs combined with OFS are occasionally administered to at-risk patients based on findings extrapolated from postmenopausal patients. The authors do not recommend offering OFS plus AI treatment to patients who are at high risk for relapse until the superiority of this combined therapy is demonstrated over standard hormone therapy with tamoxifen and/or OFS.

Conclusions

For patients with endocrine-responsive primary breast cancer who have clinical or biochemical signs of ovarian estrogen synthesis, AIs are contraindicated. Estradiol and FSH measurements should be performed before and during AI treatment in women who are not obviously postmenopausal or may be at risk for resumption of ovarian function. In perimenopausal women, tamoxifen, OFS, and OFS combined with tamoxifen are still standard strategies for adjuvant endocrine therapy.

Conflict of Interest Statement

The authors have no conflicts of interest.

Acknowledgments

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References


