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Review

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 postmenopausal 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

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Table 1
Reported incidence of amenorrhea with various chemotherapeutic regimens.

CT Regimen	Incidence of Amenorrhea by Age, %	
	<40 y	≥40 y
Anthracycline + alkylating agents	0–46	65–100
CMF based	18–61	61–97
FEC	0–38	73–88

CMF = cyclophosphamide/methotrexate/fluorouracil; CT = chemotherapy; FEC = fluorouracil/epirubicin/cyclophosphamide.
Data from Ref. 3.

turn causes an increase in ovarian production of aromatase and estrogens, as well as stimulation of estrogen-dependent tumor cells.[4,9] The use of AIs is therefore contraindicated in women with functioning ovaries.

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,[9] 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.[9,10] 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,[11] 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 chemotherapeutic regimens does not decrease the efficacy of cytotoxic treatment in premenopausal patients with hormone receptor–positive breast cancer.[12] 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.[12] 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 ($p < 0.00001$).[13]

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 42-year-old woman presented with a palpable lump in the upper outer quadrant of her right breast. The patient reported no family history of breast cancer and onset of menarche at age 14, and she had 1 child whom she breast-fed. At the time of diagnosis, the patient was considered to be premenopausal based on the occurrence of regular menses.

Mammography revealed 2 sites of microcalcifications in the right breast: 1 in the upper quadrant and 1 in the lower quadrant closer to the midline. Subsequent right modified radical mastectomy with right axillary clearance revealed a 3-cm invasive tumor (grade II). Two of 10 dissected nodes were positive, 1 with evidence of micrometastases (<1 mm). ER levels of 2 fmol/mg and progesterone receptor levels of 22 fmol/mg were measured from the patient's cytosol. Fluorescence in situ hybridization was negative for HER2/*neu*.

The patient was enrolled in Breast Cancer International Research Group Trial 005 and received 6 cycles of docetaxel (75 mg/m^2) in combination with doxorubicin (50 mg/m^2) and cyclophosphamide (500 mg/m^2). The patient reported cessation of menses after 3 months of treatment. The patient began daily adjuvant endocrine therapy with tamoxifen 20 mg in December 2002. LHRH agonist treatment was not considered because of institutional guidelines.

In April 2004 the patient was diagnosed with thrombocytopenia. Because thrombocytopenia is a potential adverse effect of tamoxifen and the patient had been amenorrheic for >12 months, the patient was switched to the steroidal AI exemestane (25 mg daily). In January 2006, exemestane treatment was discontinued because the patient reported renewed irregular menses (not considered related to tamoxifen withdrawal because 20 months of exemestane treatment had occurred). Endocrine testing in March 2006 (delayed 2 months for personal reasons) revealed postmenopausal levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (40.2 mIU/mL and 38.9 mIU/mL, respectively) with a premenopausal estradiol level of 0.626 nmol/L. Tamoxifen was reintroduced.

As of January 2007, the patient is showing no sign of recurrence or progression; however, tamoxifen was discontinued following a recurrence of grade III thrombocytopenia (platelets 43,000/mm^3) in January 2007, after 10 months of tamoxifen 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*.

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 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