Intermittent Letrozole Therapy for Metastatic Breast Cancer: Case Reports and Literature Review

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Clinical Practice Points

- Aromatase inhibitors (AIs) are considered standard first-line endocrine therapy for estrogen receptor–positive (ER^+) metastatic breast cancer in postmenopausal women. Disease resistance to AIs commonly develops during therapy. In terms of time to disease resistance, preclinical experiments indicate that intermittent treatment in responsive tumors is superior to continuous treatment, possibly owing to amelioration of putative induced mechanisms of disease resistance.
- The aim of this study was to investigate the effectiveness and safety of intermittent aromatase inhibition in patients with ER^+ metastatic breast cancer. Three patients with hormone receptor–positive metastatic breast cancer enrolled on a protocol offering intermittent letrozole treatment guided by monitoring changes in each individual's measurable serial serum CA 15-3 (carcinoma antigen 15-3) levels. One patient was on letrozole for 46 (37%) of 123 weeks of total study duration; a second patient was on letrozole for 99 (45%) of 219 weeks of total study duration; and a third patient has been on letrozole for 22 (14.8%) of 149 weeks and remains on study. As expected, toxicities during the overall study period were minimal.
- Intermittent letrozole therapy guided by serum CA 15-3 levels was well tolerated, safe, and resulted in prolonged responses and time off active therapy in the 3 cases presented. New insights into mechanisms of estrogen dependence and endocrine therapy resistance are also possible with this novel approach. Although this study closed prematurely owing to poor accrual, its results suggest that a larger proof-of-principle trial is now even more merited.

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Background

Approximately 70% of breast tumors express the estrogen receptor (ER),[1] and aromatase inhibitors (AIs) are well established as standard endocrine therapy for hormone receptor–positive metastatic breast cancer (MBC) in postmenopausal women. A pooled analysis has found a modest survival benefit favoring the AIs over other endocrine therapies in MBC (hazard ratio, 0.88; 95% CI, 0.80-0.96).[2] The standard clinical approach for the management of hormone receptor–positive MBC is to administer sequential endocrine therapy until disease progression or unacceptable toxicity.[3] Although aromatase inhibition is the most effective and well-tolerated strategy to control hormone-dependent MBC in postmenopausal women, its benefit is often limited by the development of disease resistance. For example, the median time to progression of disease on letrozole given as first-line therapy is 9 months.[4] After chronic estrogen deprivation for 1 to 6 months, breast cancer cells either can become hypersensitive to estrogen at very low concentrations or can become estrogen independent.[5,6] Using a hormone-dependent xenograft model, Sabnis et al[6,7] found that after xenograft tumors have become resistant to letrozole, a short break from letrozole for 6 weeks can induce regression of tumors again after letrozole treatment is resumed. Notably, intermittent treatment with letrozole (6 weeks on and 6 weeks off) in letrozole-responsive tumors is superior to continuous treatment, because the tumor's acquisition of treatment resistance is delayed.[6] The loss of response to AIs also contributes to the upregulation of the HER2 (human epidermal growth factor receptor 2, ERBB2)/MAPK (mitogen-activated protein kinase) pathway and downregulation of ER-α (estrogen receptor alpha)/aromatase activity. Nevertheless, with a break in antihormonal therapy, the tumors

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once again become responsive to AIs for a significant period, and overexpression of HER2 function is reversed.[6]

Tumor response after intermittent endocrine therapy in MBC is not limited to the preclinical setting. Various patient series and case reports have subsequently documented the withdrawal response after tamoxifen cessation.[8,9] AIs have much shorter half-lives than tamoxifen.[10] In contrast to cessation of tamoxifen, cessation of an AI results in rapid increases in plasma estrogen levels, back to within the pretreatment range. For this reason, the present authors believe that a response may be observed more readily after AI cessation than after tamoxifen cessation. They and others have reported cases of impressive and prolonged tumor response after cessation of AI therapy.[11,12]

This article presents 3 postmenopausal patients with ER-positive (ER^+) MBC that were enrolled on an institutional review board (IRB)–approved, phase II, multicenter clinical trial protocol (NCT00549822) evaluating intermittent AI therapy. The study opened to accrual on August 29, 2006 and closed to accrual on May 17, 2010. Owing to poor patient accrual, the study closed prematurely, before the planned enrollment of 20 patients.

Patients and Methods

This was a study of women who developed recurrent or progressive MBC while being treated with an AI. Within 2 weeks before study entry or upon study entry, all participants had to have had AI therapy discontinued and had to have been subsequently observed off all therapy while being followed up for disease response or disease stability. Women were actively followed up until progression of disease, after which they were removed from study.

At the time of study entry, or within 2 weeks of AI discontinuation (either 2 weeks before or 2 weeks after), the following were obtained: a complete medical history and physical examination; assessment of ECOG (Eastern Cooperative Oncology Group) performance status; computed tomography (CT) scans of the chest, abdomen, and pelvis; bone scans; measurements of any superficial or palpable lesions; and blood work, including liver function tests and tumor marker tests (CA 15-3 [carcinoma antigen 15-3] or CA 27.29 and CEA [carcinoembryonic antigen, CEACAM family], if available for routine use at the participating institution).

Eligible patients had to have an elevated baseline tumor marker (CA 15-3 or CA 27.29 and CEA) with either normalization or at least a reduction of 50% from peak levels after the start of AI therapy. Treatment with letrozole was restarted when tumor markers rose 25% from the nadir or, if this was still in the reference range, above the institutional upper limit of normal (ULN). Tumor markers were assessed every 4 weeks. Imaging with CT scans of the chest, abdomen, and pelvis and a bone scan was performed every 8 weeks on study and evaluated according to RECIST criteria (Response Evaluation Criteria in Solid Tumors).

Case Reports

Case 1. The patient in case 1 was a 68-year-old postmenopausal woman. At age 47, when premenopausal, she was diagnosed with a T1cN1(mic)M0, ER^+ (26 fmol/mg cytosol protein) and progesterone receptor–positive (PgR^+) (250 fmol/mg cytosol protein) carcinoma of her left breast. The primary tumor was treated with lumpectomy, adjuvant CMF (cyclophosphamide/methotrexate/5-fluorouracil) chemotherapy, and adjuvant radiotherapy. She did not receive adjuvant endocrine therapy at that time. After a disease-free interval of 17 years, at age 64, she presented with metastases in her lungs, pleura, mediastinal lymph nodes, and bones. A pleural biopsy was consistent with MBC, positive by immunohistochemistry (IHC) for ER (> 10% of nuclei stained) and PgR (> 10% of nuclei stained) and negative for HER2 by IHC and fluorescence in situ hybridization (FISH). She was started on first-line AI therapy with letrozole and monthly intravenous bisphosphonate. Before therapy, the peak CA 15-3 level was 40 U/mL (institutional ULN of 30 U/mL). After a progression-free interval of 20 months and a decline in serum CA 15-3 to 24.6 U/mL on letrozole, she enrolled in the intermittent AI protocol and stopped letrozole. She remained on observation, free of clinical disease progression as assessed by CT and bone scans for 20 weeks, until CA 15-3 rose to 33.1 U/mL. Letrozole was given for another 17 weeks, and CA 15-3 declined to normal levels. Letrozole was stopped again and she was observed off therapy for 27 weeks with slowly rising CA 15-3 levels, and after the levels peaked at 36.1 U/mL, letrozole was restarted. The patient was then on letrozole for 8 weeks, resulting in a decline in CA 15-3, and letrozole was stopped per protocol. This pattern continued for several more cycles, and the patient was on intermittent letrozole for a total of 123 weeks with stable disease by imaging as per protocol (Fig. 1). Disease progression then occurred while on letrozole, with lymphangitic spread to the lungs. She was switched to second-line endocrine therapy with fulvestrant and was free of progression for over 9 months. The worst toxicity she experienced at any time while on letrozole therapy was grade 1 hot flashes, which improved while off therapy. She was on letrozole for 46 weeks (37%) of the study duration (Fig. 2).

Case 2. The patient in case 2 was a 72-year-old postmenopausal woman who presented with metastatic cancer to the bones and pleura at age 69 years. She underwent a bone biopsy that found metastatic adenocarcinoma with signet ring features, consistent with metastasis from a primary breast cancer. Tumor cell IHC was positive for cytokeratin 7, ER (strong, diffuse staining), and PgR (multifocal) and was negative for cytokeratin 20 and HER2. Her initial CA 15-3 level was 62.8 U/mL. She was started on first-line endocrine therapy with letrozole and bisphosphonate therapy, and after approximately 16 weeks CA 15-3 declined to 26.6 U/mL. At that time, she enrolled in the intermittent AI protocol and stopped letrozole. Radiologic assessment at 8 weeks found stable disease by RECIST, but owing to an elevation of CA 15-3 by 44% to 38 U/mL and hip pain at week 12, she restarted letrozole. Letrozole was continued for 4 weeks and then was stopped after resolution of the pain and a decrease of CA 15-3 into the normal range. Subsequently, the patient had been on and off therapy with stable disease by imaging as per protocol (see Fig. 1). After a total of 196 weeks, she had an asymptomatic elevation of CA 15-3 to 33 U/mL, and letrozole was restarted. At week 199, she was hospitalized with upper gastrointestinal bleeding. Upper endoscopy found prominent gastric folds and a 2-cm ulcer but no discrete mass. Gastric biopsy found adenocarcinoma with signet ring cells, similar to the patient's initial bone biopsy, but with limited tissue available. At week 204,