Temporal Heterogeneity of Estrogen Receptor Expression in Bone-Dominant Breast Cancer: ^{18}F-Fluoroestradiol PET Imaging Shows Return of ER Expression

Erin Currin, MD[a]; Lanell M. Peterson[a]; Erin K. Schubert[b]; Jeanne M. Link, PhD[c]; Kenneth A. Krohn, PhD[a]; Robert B. Livingston, MD[d]; David A. Mankoff, MD[b]; and Hannah M. Linden, MD[a]

Abstract

Changes in estrogen receptor (ER) expression over the course of therapy may affect response to endocrine therapy. However, measuring temporal changes in ER expression requires serial biopsies, which are impractical and poorly tolerated by most patients. Functional ER imaging using ^{18}F-fluoroestradiol (FES)-PET provides a noninvasive measure of regional ER expression and is ideally suited to serial studies. Additionally, lack of measurable FES uptake in metastatic sites of disease predict tumor progression in patients with ER-positive primary tumors treated with endocrine therapy. This report presents a case of restored sensitivity to endocrine therapy in a patient with bone-dominant breast cancer who underwent serial observational FES-PET imaging over the course of several treatments at our center, demonstrating the temporal heterogeneity of regional ER expression. Although loss and restoration of endocrine sensitivity in patients who have undergone prior hormonal and cytotoxic treatments has been reported, this is, to our knowledge, the first time the accompanying changes in ER expression have been documented by molecular imaging.

J Natl Compr Canc Netw 2016;14(2):144–147

Background

Changes in estrogen receptor (ER) expression over the course of therapy may affect response to endocrine therapy. However, measuring temporal changes in ER expression requires serial biopsies, which are impractical and poorly tolerated by most patients. Functional ER imaging using ^{18}F-fluoroestradiol (FES)-PET provides a noninvasive measure of regional ER expression and is ideally suited to serial studies. Additionally, lack of measurable FES uptake in metastatic sites of disease predict tumor progression in patients with ER-positive primary tumors treated with endocrine therapy.[1–4] This report presents a case of restored sensitivity to endocrine therapy in a patient with bone-dominant breast cancer who underwent serial observational FES-PET imaging over the course of several treatments at our center, demonstrating the temporal heterogeneity of regional ER expression. Although loss and restoration of endocrine sensitivity in patients who have undergone prior hormonal and cytotoxic treatments has been reported,[5–7] this is, to our knowledge, the first time the accompanying changes in ER expression have been documented by molecular imaging.

From [a]University of Washington/Seattle Cancer Care Alliance, Seattle, Washington; [b]University of Pennsylvania, Philadelphia, Pennsylvania; [c]Oregon Health and Science University, Portland, Oregon; [d]University of Arizona, Tucson, Arizona.

Submitted July 8, 2015; accepted for publication November 30, 2015.

The authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors. This work was supported by NIH grant P01-CA42045 (K.A.K.).

Correspondence: Erin Currin, MD, University of Washington/Seattle Cancer Care Alliance, 1100 Fairview Avenue North, D5-100, Seattle, WA 98109. E-mail: ecurrin@uw.edu

Case Report

A 45-year-old woman established care after receiving adjuvant treatment at an outside institution with 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) for 4 cycles, followed by autologous bone marrow transplantation using a thiotepa and cyclophosphamide conditioning regimen for a locally advanced infiltrating lobular breast cancer characterized by a 2.4-cm primary tumor, with 12 of 12 axillary lymph nodes found to be positive at initial surgery. Histopathologic analysis of the primary lesion from a modified radical mastectomy revealed Nottingham grade II/III disease[8] with angiolymphatic invasion. Immunohistochemistry showed ER and progesterone receptor expression to be strongly positive and HER2/neu status to be negative. Chemotherapy induced menopause, and no further adjuvant endocrine or radiation therapy was administered. The clinical diagnosis of recurrent and bone-dominant metastatic breast cancer was made 6 years from her primary tumor presentation based on symptoms and multiple bony abnormalities consistent with widespread metastasis shown by multiple imaging modalities (FDG-PET [Figure 1, A], bone scan, and MRI of the spine). Bone biopsy was not performed because of a lack of an accessible nonbone site of metastasis and patient refusal. She was treated with tamoxifen and bisphosphonate therapy with symptomatic improvement, with decline in tumor extent as measured by MRI and FDG-PET (Figure 1, C). Because of promising data emerging regarding aromatase inhibitors[9] and concern about endometrial side effects, she was switched from tamoxifen to anastrozole after a year of treatment.

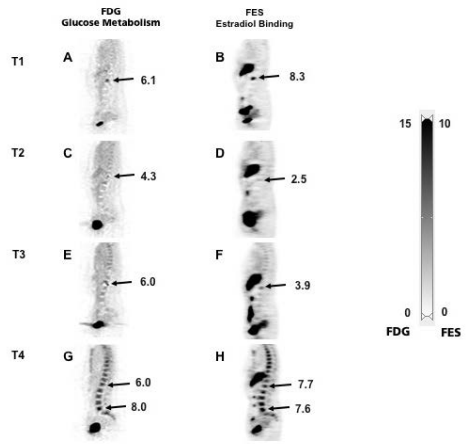

Figure 1. Temporal heterogeneity of estrogen receptor (ER) expression in Bone metastasis from an ER-positive tumor. FDG-PET (acquired as part of routine clinical care) and ^{18}F-fluoroestradiol (FES)-PET images (acquired as part of an experimental imaging study) are shown side by side to illustrate the temporal changes in uptake at 4 time points, with standard uptake values (SUVs) listed: T1, before initiation of endocrine therapy; T2, after response to endocrine therapy; T3, at subsequent disease progression on endocrine therapy; and T4, at disease progression on chemotherapy, before initiation of diethylstilbestrol (DES). At T1, the arrow shows spinal metastasis at L1 with strong uptake at initial metastatic presentation by FDG-PET (A) and FES-PET (B). The patient experienced response to endocrine therapy, as shown in T2, with a notable decrease in FDG-PET (C) and FES-PET (D). The tumor then progressed on anastrozole, shown in T3, with increasing FDG uptake (E) but less prominent FES uptake (F) compared with baseline. Her disease then responded to chemotherapy clinically (with a decrease in pain and a decline in tumor markers), but eventually progressed on chemotherapy, as shown in T4, with the emergence of diffuse spinal metastasis, as shown in 2 representative lesions by FDG-PET and FES-PET (H). This indicated an increase in the tumor's capability to bind estradiol at the time of disease progression on chemotherapy, suggesting increased ER expression. The patient subsequently experienced response to salvage endocrine therapy (DES). A grayscale is included for reference, with SUV for both FDG and FES.

The patient experienced a sustained response to endocrine therapy for 1.5 years until she began to experience increasing bone pain. New lesions were seen in the thoracic spine on MRI along with increasing tumor markers (carcinoembryonic antigen [CEA] and CA 27.29). Endocrine therapy was discontinued in favor of weekly parenteral doxorubicin and oral capecitabine (to a cumulative anthracycline dose of 850 mg/m^2) followed by single-agent capecitabine, and she experienced stable disease for 2 years based on imaging results and tumor marker levels. On subsequent progression (marrow, spine), treatment was switched to weekly paclitaxel and disease control was seen for 1 year, but then the tumor again progressed in bone and soft tissue, with worsening pain, increasing and diffuse bone and bone marrow involvement shown on FDG-PET (Figure 1, G) and MRI, increasing CA 27.29 and CEA levels, and refractory anemia, despite vinorelbine chemotherapy for what appeared to be marrow involvement of tumor.

Given the lack of visceral involvement and the patient's goal of disease palliation with minimal toxicity, endocrine therapy was resumed with diethylstilbestrol (DES), supported by prior experience suggesting a 30% to 40% response rate for late DES salvage therapy.[10,11] While on DES, the tumor marker levels declined and her anemia and pain resolved, and clinical disease control was seen for 1 year. On progression, she was treated with the combination of a steroidal aromatase inhibitor, exemestane, and fulvestrant (SERD), to which her tumor responded for more than 6 months. Her disease ultimately progressed and she eventually died.

Experimental Imaging

In addition to standard diagnostic imaging, the patient participated in observational studies using experimental imaging (FES-PET) designed to measure regional ER expression and its changes with treatment.[12] We and others have shown that FES-PET provides quantitative estimates of regional ER expression that correlate with measures of ER expression by in vitro assay of biopsy material.[13,14] FES-PET imaging was paired with FDG-PET studies to identify areas of active tumor. As shown in Figure 1, metabolic activity of spinal metastasis is depicted at 4 time points over 5 years: T1, before initiation of endocrine therapy; T2, after response to endocrine therapy; T3, at subsequent disease progression on endocrine therapy; and T4, at disease progression on chemotherapy, before initiation of DES. Notably, the patient had discontinued tamoxifen for more than 50 days before image T2, and was off of granulocyte colony-stimulating factor (G-CSF) for more than 30 days before image T4. At T1, the arrow shows spinal metastasis at L1 with strong uptake by FDG-PET (left, A, maximum standard uptake value [SUV] 6.1) and FES-PET (right, B, maximum SUV 8.3). The patient experienced response to endocrine therapy with a notable lack of FDG (left, C, maximum SUV 4.3) and FES (right, D, maximum SUV 2.5) uptake at T2, indicating reduction in tumor activity. The tumor then progressed on anastrozole (T3) with increasing FDG uptake (left, E, maximum SUV 6.0) but less-prominent FES uptake (right, F, maximum SUV 3.9) compared with baseline (T1). The tumor then responded to chemotherapy, but eventually progressed on chemotherapy (T4), with the emergence of diffuse spinal metastasis as shown by FDG-PET (left, G, maximum SUV 6.0), and diffusely high uptake on FES-PET (right, H, maximum SUV 7.7). This indicated an increase in the tumor's capability to bind estradiol at progression on chemotherapy, suggesting increased ER expression. The patient subsequently experienced a response to salvage endocrine therapy.

Discussion

Before her initial metastatic treatment, sites of bony disease showed high FES uptake, indicating robust ER expression. With successful endocrine therapy, both FDG and FES uptake were lower, indicating tumor regression. At the time of progression on an aromatase inhibitor, FDG uptake again increased; however, FES uptake at the same site was both qualitatively and quantitatively lower than it had been before the initiation of endocrine treatment, suggesting lower ER expression. Finally, after progression on sequential chemotherapy, both FDG-PET and FES-PET showed high uptake diffusely in bone and marrow, indicating active disease with high ER expression. These images show, quantitatively and qualitatively, the presence, decline, and then recrudescence of ER expression in this heterogeneous breast cancer.

Observational experimental imaging studies to measure regional ER expression over the disease course suggest a possible mechanism for clinical findings. The emergence of endocrine resistance was accompanied by an apparent decrease in FES uptake compared with studies before endocrine therapy, and suggested a relative loss of ER expression. Interestingly, images acquired after response and then progression showed high FES uptake at all sites of disease, suggesting a reemergence of disease with high ER expression. One hypothesis to explain these findings is that the treatments selected for a particular phenotype. Endocrine therapy would select for cells with lower ER expression, which are more likely to be hormone-independent. On the other hand, some studies have suggested that ER-expressing cancers may be less sensitive to cytotoxic chemotherapy,[15] which would select for cells with high ER expression.

In this case report, the imaging studies were observational and not used for treatment decision-making. Nevertheless, these results confirm temporal heterogeneity of ER expression over the course of systemic treatments and show the unique capability for molecular imaging methods to assess change in regional ER expression in breast cancer, which merits further study.

References

1. van Krutchen M, de Vries EG, Brown M, et al. PET imaging of oestrogen receptors in patients with breast cancer. Lancet Oncol 2013;14:e465–475.
2. Linden HM, Stekhova SA, Link JM, et al. Quantitative fluoroestradiol positron emission tomography imaging predicts response to endocrine treatment in breast cancer. J Clin Oncol 2006;24:2793–2799.
3. Dehdashti F, Mortimer JE, Trinkaus K, et al. PET-based estradiol challenge as a predictive biomarker of response to endocrine therapy in women with estrogen-receptor-positive breast cancer. Breast Cancer Res Treat 2009;113:509–517.

4. van Kruchten M, de Vries EG, Glaudemans AW, et al. Measuring residual estrogen receptor availability during fulvestrant therapy in patients with metastatic breast cancer. Cancer Discov 2015;5:72–81.
5. Ellis M, Naughton MJ, Ma CX. Treatment approach to metastatic hormone receptor positive breast cancer: endocrine therapy. Available at: http://www.uptodate.com/contents/treatment-approach-to-metastatic-hormone-receptor-positive-breast-cancer-endocrine-therapy. Accessed October 6, 2015.
6. Gradishar WJ, Anderson BO, Balassanian R, et al. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 3.2015. Available at: NCCN.org. Accessed October 6, 2015.
7. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520–529.
8. Elston CW, Ellis IO. Pathologic prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991;19:403–410.
9. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60–62.
10. Ingle JN, Ahmann DL, Green SJ, et al. Randomized clinical trial of diethylstilbestrol versus tamoxifen in postmenopausal women with advanced breast cancer. N Engl J Med 1981;304:16–21.
11. Lonning PE, Taylor PD, Anker G, et al. High dose estrogen treatment in postmenopausal breast cancer patients heavily exposed to endocrine therapy. Breast Cancer Res Treat 2001;67:111–116.
12. Linden HM, Stekhova SA, Link JM, et al. Quantitative fluoroestradiol positron emission tomography imaging predicts response to endocrine treatment in breast cancer. J Clin Oncol 2006;24:2793–2799.
13. Mintun MA, Welch MJ, Siegel BA, et al. Breast cancer: PET imaging of estrogen receptors. Radiology 1988;169:45–48.
14. Peterson LM, Mankoff DA, Lawton T, et al. Quantitative imaging of estrogen receptor expression in breast cancer with PET and 18-F fluoroestradiol. J Nucl Med 2008;49:367–374.
15. Carey LA, Dees EC, Sawyer L, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 2007;13:2329–2334.