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Letrozole withdrawal response in locally advanced breast cancer

Antiestrogen therapies are among the most effective breast cancer treatments. Third generation aromatase inhibitors are superior to tamoxifen in both early and advanced breast cancer patients. Despite the endocrine sensitivity of the majority of breast tumors, a significant proportion of patients experiences disease progression due to either an inherently intrinsic or acquired resistance to endocrine agents. Therefore, a common clinical practice is the sequential use of different hormonal treatments.

We describe the case of a 77-year-old female presented with a locally advanced breast cancer of the upper outer quadrant of the left breast, which measured 3 × 3.5 cm; an enlarged, fixed axillary node of 3 cm in diameter was palpated (T2 N2a, clinical stage: IIIA). Tumor biopsy showed an infiltrating ductal carcinoma, with a positive staininig for estrogen receptor (ER) and progesterone receptor (PgR) (ER: 99%, PgR: 93%), a high proliferative index (Ki67: 38%), and without overexpression of Her2-neu. The positron emission tomography/computed tomography (PET/CT) evaluation showed high metabolic activity in both the breast [maximum standardized uptake value (SUVmax): 5.6] and the axillary node (SUVmax: 6.5). The main comorbidity of the patient was a hepatitis C virus (HCV)-related cirrhosis: she had elevated liver function tests [aspartate aminotransferase : 160 U/l; alanine transaminase : 123 U/l; γ-glutamyltransferase (γ-GT): 111 U/l; alkaline phosphatase : 279 U/l; total bilirubin: 1.48 mg/dl], bleeding disorder [quick value: 45%; international normalized ratio : 1.63], thrombocytopenia (platelet count: 40 000), and the presence of HCV in the blood (quantitative HCV-RNA: 677 000 UI/ml). Because of her clinical condition and the local extension of the tumor, the surgical resection was not possible. Treatment with letrozole 2.5 mg/die was initiated with close monitoring of liver function. After 8 months of therapy, a complete response was documented both by clinical examination and by PET/CT, which showed the disappearance of the previous sites with high metabolic activity. After 4 months, clinical disease progression was observed with a volume increase of both the breast and the axillary node. Letrozole was discontinued and, due to the worsening of her liver function, no second-line anticancer therapy was initiated. After 2 months, despite the absence of anticancer treatment, a complete clinical response was observed with the disappearance of the breast and axillary node lesions: she continues to have a complete sustained withdrawal response on 10 months later.

A withdrawal response to antihormonal therapy is a potential therapeutic maneuver for patients with progressive prostate cancer (antiandrogen withdrawal) [1], while only few cases have been reported in the literature for breast cancer. Tumor response after withdrawal of tamoxifen was first described by Legault-Poisson et al. [2] and then in other two cases [3, 4]; two cases of aromatase inhibitor withdrawal response in metastatic breast cancer have been reported [5, 6]. Bhide and Rea [5] reported a case of complete response after exemestane withdrawal in a patient with a metastasis in the supraclavicular fossa, and Cigler and Goss [6] described a partial response in bone and liver metastasis after withdrawal of goserelin and letrozole combination. In both the above reported cases, a response to aromatase inhibitor withdrawal was observed in patients with metastatic breast cancer previously treated with three or more lines of antihormonal therapies.

Here, we report the withdrawal response to letrozole alone in a patient with locally advanced breast cancer who didn't receive any previous anticancer therapy.

There are some preclinical data, both *in vitro* and in mouse xenograft models [7, 8], that support a rationale to use antihormonal therapy withdrawal in the treatment of breast cancer. As postulated by Song et al. [9], long-term estrogen deprivation sensitizes breast cancer cells to proapoptotic effects of reintroduction of low doses of estradiol, which are normally only seen at higher doses; the extremely low-estrogen environment encountered in the presence of antihormonal therapy may sensitize the tumor cells to low estrogen levels found in postmenopausal women after antihormonal therapy withdrawal: these low levels of estrogen may be sufficient to induce a tumor response.

Antihormonal therapy withdrawal could be considered a therapeutic measure, at least in some selected patients, such as patients treated with two or more hormone therapies with a good clinical response before disease progression and without life-threatening metastases. A short duration of aromatase inhibitor or tamoxifen withdrawal may be considered before starting additional anticancer treatment.

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disclosure

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