The majority of breast cancers in male patients are hormone receptor positive. Tamoxifen has proven to be successful in both adjuvant and metastatic settings and remains the standard of care. Given the improved outcomes in female patients with aromatase inhibitors (AI), these drugs have become a potential therapeutic tool for male patients. Preliminary data show effective suppression of oestradiol levels in males treated with AI and some reports have demonstrated objective responses. Here we report a case of a male patient with metastatic breast cancer treated with letrozole who achieved clinical response associated with a decrease in blood oestradiol levels.

**Key words** Male • Breast neoplasm • Aromatase inhibitor • Letrozole • Oestradiol


**Case**

A 51-year-old man presented to the Royal Marsden Hospital in September 2003 with a clinically multifocal carcinoma on his left breast, confirmed on fine needle aspirate cytology, with the largest nodule measuring 14x9 mm, and small palpable axillary lymph nodes. His past medical history included a psychiatric history of phobia (facial hair phobia) that had been treated at the age of 20 with cyproterone acetate and conjugated oestrogens (Premarin®) for one year. He had a fine needle aspiration, which was diagnostic for carcinoma. His serum oestradiol was 200 pmol/l. Testosterone level was 25.9 nmol/l and luteinising hormone (LH) was 6 u/l. The patient declined treatment until December 2005, when he represented with an 8x7 cm hard mass on his left breast without skin involvement and palpable left axillary, bilateral cervical and submandibular lymphadenopathy. A core needle biopsy confirmed grade 2, invasive ductal carcinoma, without lymphovascular invasion, oestrogen receptor positive 8/8, progesterone receptor positive 8/8 and HER-2 negative. A computerised tomography (CT) scan confirmed these areas of nodal involvement and lytic bone metastases in cervical vertebrae C6–C7.

Treatment with tamoxifen was recommended but refused and at the patient’s insistence he started treatment with letrozole 2.5 mg daily in January 2006. He also received radiotherapy to his involved cervical vertebrae for neurological symptoms.

After 2 months of treatment, a good clinical response was achieved with the disappearance of the cervical nodes, clinical regression of his other lymphadenopathy and a decrease in size of the breast primary to 3.4x3.8 cm. A follow-up CT scan showed reduction in all lymphadenopathy and the breast mass, confirming a partial response. The serum oestradiol after 3 months on treatment was 11 pmol/l. Testosterone was 30.4 nmol/l and LH was 6 u/l.

**Discussion**

Male breast cancer is a rare disease and accounts for less than 1% of all breast cancer patients in Europe [1]. Risk factors for male breast cancer include a positive family history of either male or female breast carcinoma, and 4–40% of cases have been linked to inherited mutations (BRCA-2, AR gene, cytochrome P45017, XXY karyotype, the PTEN suppressor gene associated with Cowden syndrome and the CHEK2 gene) [2]. In addition, conditions leading to hyperoestrogenism including obesity [3] and exogenous oestrogen administration [4] have also been associated with male breast cancer. Our patient’s unusual exposure to oestrogen at a young age may have influenced the development of his breast tumour.

Oestrogen production in men has a role during puberty and adult life. Men have plasma oestradiol levels above the female postmenopausal range [5], presumably because of the much higher levels of androgenic substrates for peripheral aromatisation [6]. The sources for
oestrogen include the testes, which produce approximately 15% of the total amount and seem to have an important role in spermatogenesis [7], and extragonadal production that results from the conversion of circulating testosterone through the enzyme aromatase mainly in subcutaneous fat. Oestrogen is of importance for the development and maintenance of other organs like the bone [8] and the brain [9].

The level of testosterone in men decreases with age, but it is still sufficient to maintain a highly significant production of oestrogen, at levels that protect men from diseases caused by oestrogen deprivation [6].

Male breast cancer is hormone receptor (HR) positive in a high percentage of cases (around 90%) [10] and endocrine therapy has therefore been used as a therapeutic approach in this disease. In the adjuvant setting, tamoxifen improves disease-free and overall survival and is considered the standard of care [11].

In the metastatic setting, various treatments have been tested. Orchiectomy was the first treatment to show efficacy [12]. Other ablative techniques, like adrenalectomy and hypophysectomy, were explored, with response rates over 50%, but with significant morbidity [13]. These techniques are now rarely used and have been substituted by additive hormonal therapy.

A variety of agents have been tested: in a series of 55 retrospectively assessed patients, diethylstilbestrol achieved a 38% rate of objective response with a median duration of response of 7 years [14]; cyproterone alone or in combination with busertelin showed objective responses (around 60%) with a median duration of 8–11.5 months [15, 16].

A number of case reports evaluating other hormonal therapies (LHRH agonist and flutamide [17], medroxyprogesterone [18] androgens [19]) also showed objective responses and good tolerance with these treatments. Some studies showed increased efficacy in patients with prior orchiectomy [18, 20], although this was not confirmed in another series [19].

Tamoxifen has been the main hormonal treatment for female patients until recently. It has been evaluated in male patients showing good response rates (25–48% in small series) and seems to be related to oestrogen receptor status [21–23]. It is now recommended as first-line endocrine therapy for men with breast cancer [24].

In women recent trials have demonstrated that third-generation aromatase inhibitors (AI) are superior in efficacy to tamoxifen for postmenopausal women in the metastatic and adjuvant settings [25–28]. This offers the possibility that these agents may also be effective against male breast cancer.

A number of studies assessing the hormone level alterations in males treated with AI have been reported. A series of five men with advanced breast cancer treated with the first generation AI aminoglutethimide showed suppression of oestradiol levels in all patients [20]. In healthy males, treatment with the non-steroidal AI (NSAI) fadrozole hydrochloride caused a significant fall in plasma oestradiol and significant increase of testosterone and follicle stimulating hormone (FSH) [29]. These findings have been consistently confirmed in further studies with the NSAI letrozole [30] and anastrozole [31]. In one of the studies [31] the oestradiol suppression was sustained over 10 weeks and levels of LH and FSH were both increased significantly after treatment. These data support the efficacy of AIs in oestradiol suppression and provide a biological rationale for the testing of these treatments in male patients.

The increase in LH levels consistently reported is due to part of the feedback from gonadal testosterone being due to its aromatisation in the hypothalamus. This results in increased testicular testosterone synthesis and higher testosterone levels. In our patient we saw no increase in LH levels but this was in blood samples taken 2 years apart. Despite this, we saw a modest increase in testosterone levels consistent with these earlier reports.

So far no formal trials have been published but a few case reports have reported clinical activity [32, 33]. In one study, 5 patients who had previously received tamoxifen were treated with anastrozole with stabilisation of disease in 2 of the patients but no objective response [32]. Two patients treated with letrozole both showed clinical response [33, 34], in addition to ours. Letrozole is a more profound inhibitor of circulating oestrogens than anastrozole [34] but further study is required to determine whether this might lead to increased clinical efficacy.

A theoretical concern with aromatase inhibitors in men is the elevation of LH and FSH and testosterone with the AI treatment seen in the healthy male trials [29, 31], as this might induce increased oestradiol production in the testes and thus incomplete oestrogen suppression. Notably, the on-treatment oestradiol level in our patient was 11 pmol/l, which would be a high value in a postmenopausal woman. There is a potential benefit of castration in addition to AIs, as both testicular and non-testicular sources of oestrogen would be targeted. This hypothesis is being tested in a prospective study by the Southwest Oncology Group, which is assessing the efficacy of the combination of anastrozole and goserelin (a gonadotropin-releasing hormone analogue) [35].

In conclusion, this is the first comprehensive report of both clinical outcome and biochemical study in a male breast cancer patient treated with letrozole and adds to the growing evidence that aromatase inhibitors may play a valuable role in the treatment of male patients with breast cancer, providing a further treatment option in addition to tamoxifen.