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Successful Use of Letrozole in Male Breast Cancer: A Case Report and Review of Hormonal Therapy for Male Breast Cancer

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Male breast cancer is an uncommon occurrence. Treatment of male breast cancer is typically extrapolated from data on the treatment of female breast cancer. Recently, aromatase inhibition has been proven as an effective therapy for female breast cancer, particularly in the setting of advanced cancers. The efficacy of aromatase inhibitors in males, however, has not been established. We report the successful treatment of a male with locally advanced breast cancer using the aromatase inhibitor letrozole.
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KEY WORDS: male breast neoplasms; aromatase inhibitors

INTRODUCTION

Male breast cancer is a rare disease, accounting for less than 1% of all breast neoplasms. In Canada, the age-standardized incidence of breast cancer in males is just under 1 per 100,000 [1]. Patients tend to present later and with a more advanced tumor, thus prognosis is often poorer [2]. Due to the overall small numbers of breast cancer in males there is a dearth of information regarding optimal treatment methods. In most cases treatment modalities have been extrapolated from protocols used to treat women with breast cancer.

Recently, when compared to tamoxifen, aromatase inhibitors have been shown to provide a superior disease-free survival advantage in post-menopausal women who have completed primary therapy [3]. As well, aromatase inhibitors have shown a significant impact in the treatment of advanced female breast cancer as both first-line therapy [4–6] and as neoadjuvant therapy [7,8]. To our knowledge, however, there are no prospective trials addressing the efficacy of selective aromatase inhibitors in male breast cancer. Case reports alone have outlined the use of the third generation aromatase inhibitors anastrozole and letrozole [9–11]. The response to anastrozole has been limited [9,10]. Letrozole, on the other hand, has been reported to induce remission after failure of tamoxifen [11].

In this study we report a case of an unresectable breast cancer, in a male patient, which responded to therapy with letrozole, and review the literature on hormonal manipulation in the treatment of male breast cancer.

CASE

An 87-year-old man presented to the Cedars Breast Clinic of the McGill University Health Centre in February 2003, with a 6×6.5 cm fixed mass in the left breast. His past medical history included mild to moderate Alzheimer's disease, hypothyroidism, hypertension, and severe coronary artery disease necessitating a double coronary artery bypass graft with aortic valve replacement. In addition, he had previously undergone resection of a squamous cell carcinoma of the tongue (with no evidence of recurrence to date). The mass had been painlessly growing for 1 month. On examination there was no nipple discharge, nor were there any skin changes. He had no evidence of lymphadenopathy. Fine-needle aspiration cytology and core-needle biopsy were both performed. Final pathology confirmed the presence of an invasive ductal carcinoma, grade II/III, positive for

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estrogen and progesterone receptors, and negative for Her-2-neu.

Given the patient's co-morbidities, surgical intervention was deferred and the patient was started on letrozole at a dose of 2.5 mg per day in April 2003. On subsequent follow-up visits the mass was noted to have substantially decreased in size measuring 3×2.5 cm in July 2003, 2×2.5 cm in October 2003, and 1×1 cm. in April 2004. Currently, after approximately 12 months of treatment, the patient continues to do well and has no clinical evidence of metastatic disease.

DISCUSSION

Breast cancer in men is an uncommon disease, accounting for less than 1% of all breast cancers. In general, the recommended therapy for male breast cancer is similar to that for female breast cancer. Surgery, usually modified radical mastectomy, is the mainstay of treatment, however, the successful application of lumpectomy and radiotherapy has been reported [12]. Adjuvant chemotherapy has successfully been applied to node-positive disease [2,13–16]. Hormone manipulation with tamoxifen has also found success in the adjuvant setting [2,16,17].

Despite parallels in treatment, male breast cancer is different from the female variety in many ways. Risk factors for the development of breast cancer in men vary from those in women as they are not tied to childbearing. In men, obesity, family history, and lack of physical activity are the important risk factors for the development of breast cancer, whereas increased activity appears to be associated with a decreased risk [18]. Male breast cancer also appears to differ from female breast cancer in that it more often over-expresses estrogen receptors—a finding that does not apply to progesterone receptors or Her-2/neu [19]. This implies an important role for circulating estrogens. It may also help explain the increased risk of cancer in obese males, as the most significant site of aromatization is the adipose tissue [20]. Endogenous estrogens, produced by the peripheral aromatization of androgens, provide a stimulus for a growing cancer rich with estrogen-receptors. Improved understanding of the role of estrogens in male breast cancer has opened up new opportunities for therapeutic intervention, especially in the form of hormonal manipulation.

In men approximately 80% of circulating estrogen is derived from peripheral aromatization of androgens with the remaining 20% secreted directly by the testes [20]. Early attempts to control hormones as a treatment of male breast cancer were focused on complete removal or ablation of potential sources of hormones. Initially, orchiectomy was tried. First performed in 1942 as a treatment for metastatic male breast cancer, this procedure did result in regression of bony metastases [21]. Since then several case series have shown response rates of 30%–50% when orchiectomy is used to treat advanced breast cancer in males [22–24]. In the face of disease progression after orchiectomy, the adrenals were often the next to be removed. Again, case series demonstrated successful control of disease in up to 80% of patients [23]. Ablative techniques went as far as hypophysectomy, in an attempt to control the central stimulation of hormone production. Success rates over 50% were achieved with this technique [22]. Ablative techniques rely on surgery to permanently remove those organs responsible for sex-hormone production. These procedures have the potential to be complicated by deleterious side effects. Problems can occur, not only secondary to the surgery itself, but also as a result of the loss of other key products of these organs such as testosterone (in the case of orchiectomy) and cortisol (in the case of adrenalectomy). Furthermore, orchiectomy can be psychologically difficult to deal with.

Given the serious side effects of the ablative techniques other means of hormone manipulation have been tried. Several reports exist showing mild to moderate success with a variety of agents. Estrogen therapy in the form of diethylstilboestrol has been shown to have a 38%–40% total response rate when given to patients with advanced or recurrent male breast cancer [25,26]. Cyproterone acetate, a synthetic steroid with antiandrogenic and progestational activity has also shown success. One case series of three patients with advanced male breast cancer demonstrated partial remission in one patient and complete remission in the remaining two [27]. Other studies have found slightly lower success rates for males with advanced cancers, with 18% of patients showing complete response and 45% showing a partial response [26]. Other hormones with progestational activity have demonstrated mixed results. Medroxyprogesterone acetate has been shown to have had success (complete and partial responses) in five of six male patients with advanced cancers [28]. No response was noted in two males with advanced cancer treated by Muggia et al. [29]. This latter trial may have not have had the same outcome because the doses of medroxyprogesterone acetate utilized were much lower. A marked improvement in effect has been demonstrated in females with advanced breast cancer when higher doses of medroxyprogesterone acetate were employed [30]. Other reports of high-dose medroxyprogesterone acetate in advanced male breast cancer, though, have not shown any response at all [26]. Androgens too, have been used with varying results. Success with androgens in advanced breast cancer in males has ranged from 0% to 60% [24,26]. All of the successes demonstrated by these various hormone manipulations were comparable to the success achieved

with orchiectomy. The results should be treated with caution, however, as they have all been demonstrated in case series with small patient numbers. Comparative studies between any of these therapies have not been reported.

It was recognized, given the high number of male breast cancers positive for the estrogen-receptor, that tamoxifen might be a valuable therapeutic intervention. Initial trials demonstrated success in cases of advanced male breast cancer. Response rates ranging from 25% to 48% have been published [24,26,31]. In addition, tamoxifen has been shown to be effective as an adjuvant treatment. Increases in 5-year disease-free survival from 28% to 56% have been observed in patients with male breast cancer [17]. In the same study, 5-year overall survival was improved from a rate of 44% in historical controls to 61% in males treated with adjuvant tamoxifen [17]. The success of tamoxifen has led to its incorporation as a standard therapy in male breast cancer.

Estrogen control can be attained either by blocking the receptors for estrogens (as with tamoxifen) or by blocking the production of estrogens (Fig. 1). The final step in the production of estrogens in post-menopausal women and in 80% of circulating estrogens in men is the peripheral aromatization of the circulating androgens [20]. This step is performed by the enzyme aromatase. Aromatase inhibition was first achieved using the anticonvulsant aminoglutethimide. Case reports with small numbers have demonstrated poor results when aminoglutethimide has been applied to advanced male breast cancer. In one series by Lopez et al. only two of five patients had a response (one partial and one complete response) [26]. In another series by Harris et al. only one of five patients had a response. The one success was in a patient with a previous orchiectomy [32].

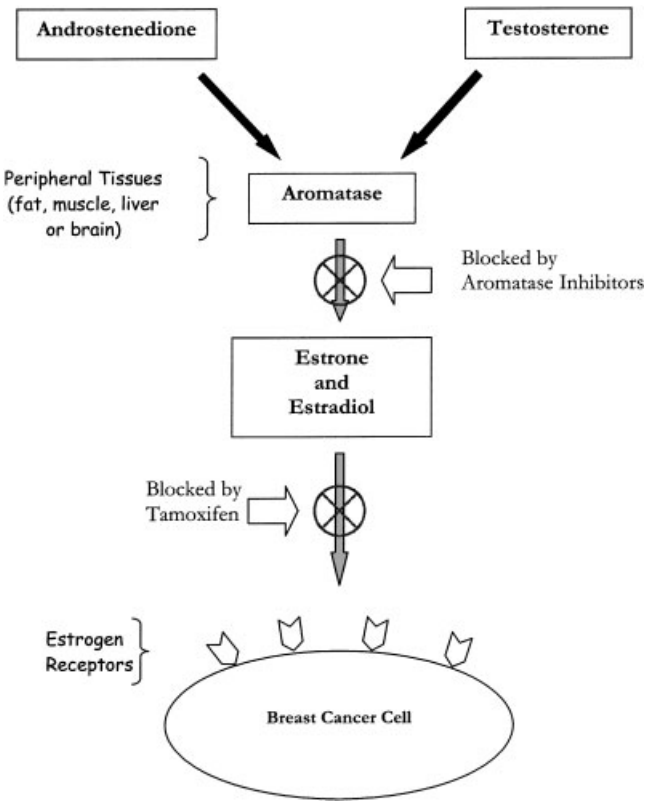

Fig. 1. The effects of estrogens on breast cancer cells can be diminished by either blocking estrogen receptors in those cells with tamoxifen or by blocking estrogen production with an aromatase inhibitor.

Recent advances have led to the development of the third generation of aromatase inhibitors. Studies comparing these drugs to tamoxifen in the treatment of breast cancer in women have shown great promise. In the adjuvant treatment of female breast cancer, anastrozole has shown superior disease-free survival compared to tamoxifen [3]. Both anastrozole and letrozole have been shown to be as good as, if not better than, tamoxifen as first-line therapy in advanced cancers [4–6]. Finally, in the neoadjuvant setting, letrozole has been shown to be more efficacious than tamoxifen [7,8].

Following the success of aromatase inhibition in females, attempts have been made to use these drugs in male patients with breast cancer. In a recent study of five male patients with metatstatic breast cancers, three of the five patients responded to anastrozole. Those patients who responded experienced disease stabilization for up to 8 months. The other patients had progressive disease despite the use of anastrozole [9]. Additionally, a single male patient has been reported to have responded completely to the use of letrozole for the treatment of a recurrent metastatic breast cancer. This complete remission was induced after a partial regression with tamoxifen therapy [11].

Giordano et al. have expressed doubts regarding the success of aromatase inhibition compared to other hormonal therapies. They cite the poor performance of aminoglutethimide in addition to the lackluster performance of anastrozole in their own series [9]. It has been suggested that aminoglutethimide is only effective in patients with a previous orchiectomy [31]. Others, however, have reported success with this drug without prior orchiectomy [26]. Aminoglutethimide does lower circulating estrogens in males [31]. The question remains, though, if this decrease is enough to allow aminoglutethimide to be clinically useful. This question may in fact be irrelevant, as the third generation aromatase inhibitors are known to be three magnitudes of order more potent than aminoglutethimide [33]. This increased potency has translated into an overall increased degree of aromatase inhibition and subsequent clinical efficacy versus aminoglutethimide [34]. Interestingly, this comparison has been documented between

aminoglutethimide and letrozole alone. Indeed, it has been suggested that anastrozole may not provide the same degree of aromatase inhibition and therefore, is not as effective as letrozole in lowering circulating estrogens [35]. Further indirect evidence of the superiority of letrozole over anastrozole can be found in those trials which have evaluated the efficacy of either anastrozole or letrozole versus tamoxifen in the primary treatment of advanced breast cancers. These studies have shown a definite benefit of letrozole compared to tamoxifen, whereas anastrozole has only shown equivalence [4–8]. Perhaps letrozole is the superior aromatase inhibitor choice for the primary treatment of advanced breast cancer. This concept should be viewed cautiously in the treatment of advanced male breast cancer as the current evidence has been gathered from female patients alone. Confirmatory studies in the male population are needed.

Given the excellent response of women to the aromatase inhibitors, they are being increasingly considered for males with breast cancer. Here we have reported the first case of letrozole as primary therapy for a male patient with an unresectable breast cancer. The dramatic response of the tumor to therapy provides some evidence that aromatase inhibition may be an appropriate treatment for men with advanced tumors. The use of aromatase inhibitors has the potential to effectively convert a non-operable tumor into an operable one, or even result in the complete regression of the tumor. The apparent promise for the use of letrozole specifically, underscores the need for further trials in larger populations.

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