Endocrine therapy for male breast cancer: rates of toxicity and adherence

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ABSTRACT

Purpose

Most male breast cancer tumours are hormone receptor–positive; the patients therefore receive endocrine therapy. There is, however, a paucity of published data on toxicities experienced by male breast cancer patients who are prescribed endocrine therapy. In the present study, we examined rates of adherence to and toxicity from endocrine treatments in male breast cancer patients treated at a single institution.

Patients and Methods

We conducted a retrospective study of male patients diagnosed with breast cancer at The Ottawa Hospital Cancer Centre during 1981–2003. Data collected included patient age, hormone receptor status, therapy adherence, self-reported toxicities, and type and duration of endocrine therapies.

Results

The review located 59 cases of early-stage and metastatic male breast cancer. Median patient age was 68.0 years. Tamoxifen was given to 38 patients (64.4%), anastrozole to 8 (13.6%), and letrozole to 5 (8.5%). Of patients who received endocrine therapy, 10 (25%) received adjuvant systemic chemotherapy. Toxicity was reported by 19 patients taking tamoxifen (50%), with hot flashes being the most common complaint (18.4%). Decreased libido, weight gain, and malaise were reported by 5 patients (13.2%). Rash and erectile dysfunction were reported by 3 patients (7.9%). Increased liver enzymes, pulmonary embolism, superficial thrombophlebitis, myalgia, depression, visual blurring, and loose stools were each reported in 1 patient (2.6%). Tamoxifen therapy was discontinued secondary to toxicity in 9 patients (23.7%). Of the patients treated with anastrozole, 3 (37.5%) reported toxicity, with 1 report each of decreased libido, leg swelling, and depression (12.5%). Toxicity was reported in 2 patients taking letrozole (40%), with both reporting peripheral edema, and 1 reporting hot flashes. No patient discontinued anastrozole or letrozole because of toxicity.

Conclusions

Few studies specifically report data on adherence to and toxicities from endocrine therapies in male breast cancer patients. The rate of discontinuation at our institution because of toxicity (23.7%) is similar to that reported in the female breast cancer population. Future prospective studies should explore strategies to improve adherence to endocrine therapy in this population.

KEY WORDS

Endocrine therapy, tamoxifen, anastrozole, male breast cancer, toxicity, adherence

1. INTRODUCTION

Male breast cancer constitutes up to 1% of all breast cancer cases and 1% of all cancer cases in men. More than 90% of male breast cancer cases are infiltrative ductal carcinomas [1–5], with 80%–90% expressing the estrogen receptor and 65%–92% expressing the progesterone receptor [3,4,6–8]. Given this receptor profile, endocrine therapy is often prescribed in this patient population. Tamoxifen, a selective estrogen receptor modulator, has been shown to be clinically effective in male breast cancer patients with endocrine-responsive metastatic breast cancer [9,10], thus leading to its incorporation into standard clinical practice.

Aromatase inhibitors (AIs) represent a new treatment option for postmenopausal women with hormone-sensitive breast cancer. These drugs, which prevent the conversion of androstenedione to estradiol, have been shown to benefit women with advanced and early-stage disease alike [11–14]. Given the success of the AIs in those settings, clinicians are considering the potential benefit of AIs in the male breast cancer population.

Physiologically, 80% of circulating estrogen in men is produced by the aromatase pathway; the remaining 20% is produced directly in the testes [15,16]. It has therefore been postulated that aromatase inhibition alone would be insufficient for treating estrogen receptor–positive male breast cancer, possibly leading to an increase in serum estrogen [17]. Nonetheless, studies have demonstrated that the use of AIs in men can lead to a decrease in serum levels of estradiol [18], and cases of clinical response to AIs in locally advanced and metastatic male breast cancer have been reported [19–22].

The toxicities of tamoxifen and AIs in women with breast cancer have been reported in the clinical and nonclinical trial settings. In contrast, however, limited information is available on the toxicities of these agents in the setting of male breast cancer. Early studies evaluating the efficacy of tamoxifen in male breast cancer reported few side effects to tamoxifen [23,24]. A later article reported 2 cases of impotence secondary to tamoxifen treatment [25], but to our knowledge, only one study of tamoxifen toxicity in male breast cancer has been published [26]. Contrary to what had previously been reported, tamoxifen treatment in men with breast cancer was associated with a high rate of treatment-limiting side effects, with approximately 20% of patients discontinuing treatment prematurely. Adverse effects included loss of libido, weight gain, and hot flashes. Data concerning the toxicity of AIs in male breast cancer patients are even more limited: no published studies are dedicated to this topic.

We retrospectively evaluated toxicities and adherence rates in male breast cancer patients treated with endocrine therapy at a tertiary care cancer centre.

2. PATIENTS AND METHODS

Our study was approved by The Ottawa Hospital research ethics board. All male breast cancer patients (early-stage and advanced) presenting to The Ottawa Hospital Cancer Centre from 1981 to 2003 were included in the analysis. Data collected included patient age, tumour histology, hormone receptor expression, and surgical and systemic treatment. Information on self-reported side effects of endocrine treatments and discontinuation of endocrine treatments, as documented in patient visit records, was recorded.

3. RESULTS

Data were available for 59 cases of breast cancer in men. Tables I and II outline characteristics of the patients and their treatment. Of the 59 patients reviewed, 42 (71.2%) were treated with endocrine therapy. Specifically, 29 patients received tamoxifen treatment alone, 2 patients received anastrozole, and 6 patients received both tamoxifen and anastrozole at different times during their treatment. Tamoxifen and letrozole were both given to 5 patients at different times during

TABLE I Characteristics of patients treated with endocrine therapy

Characteristic	*Value*
Patients treated (*n*)	42[a]
Age (years)	
Median	68.0
Range	46–84
Tumour histology (*n*)	
Infiltrating ductal carcinoma	38
Papillary carcinoma	1
Synchronous infiltrating and lobular carcinoma	1
Stage at diagnosis (*n*)	
I	12
II	21
III	5
IV	2
Tumour size (*n*)	
T1	23
T2	11
T3	0
T4	6
Axillary nodal status (*n*)	
Positive	20
Negative	15
Unknown	5
Estrogen receptor (*n*)	
Positive	31
Negative	2
Unknown	7
Progesterone receptor (*n*)	
Positive	28
Negative	3
Unknown	9
Primary surgery (*n*)	
Modified radical mastectomy	32
Segmental mastectomy	1
Total mastectomy	2
Simple mastectomy without maxillary node evaluation	5
Adjuvant radiation therapy (*n*)	
Yes	15
No	25

[a] Two patients were excluded from the analysis because of incomplete data.

TABLE II Systemic treatments in patients treated with endocrine therapy

Treatment	*(n)*
Adjuvant chemotherapy	
Yes	10
No	30
Setting of initial tamoxifen treatment	
Adjuvant	30
Metastatic	7
Post local recurrence	1
Setting of initial anastrozole treatment	
Adjuvant without prior tamoxifen treatment	2
Adjuvant with prior tamoxifen intolerance	1
Metastatic with prior tamoxifen treatment	5
Setting of initial letrozole treatment	
Metastatic with prior tamoxifen treatment	5

TABLE III Discontinuation of tamoxifen treatment secondary to toxicity

Pt	*Toxicities leading to discontinuation*	*Time on treatment (months)*
1	Pulmonary embolism	54
2	Hot flashes	38
3	Decreased libido, weight gain, rash	15
4	Fatigue, rash	2
5	Fatigue, hot flashes, visual blurring	10
6	Myalgia	2
7	Hot flashes, erectile dysfunction, decreased libido, weight gain	51
8	Fatigue, decreased libido, hot flashes, weight gain	25
9	Rash	1

Pt = patient.

their treatment. Two patients who received tamoxifen were excluded from our study because follow-up data beyond the date of prescription were not available. Hence data from a total of 40 patients were included in the final analysis.

3.1 Tamoxifen Therapy

In 38 men with breast cancer, tamoxifen treatment continued for a median of 35.5 months (range: 1–120 months). Of those 38 patients, 19 (50%) reported 1 or more adverse effects from tamoxifen. Hot flashes, the most common toxicity, were reported by 7 patients (18.4%). Weight gain, fatigue, and decreased libido were each reported by 5 patients (13.2%). Erectile dysfunction and rash were each reported by 3 patients (7.9%). Increased liver enzymes, pulmonary embolism, superficial thrombophlebitis, depression, visual blurring, and loose stools were each reported in 1 patient (2.6%). In 9 patients (23.7%), tamoxifen treatment was discontinued because of toxicity after a median treatment time of 15 months (range: 1–54 months; Table III).

3.2 AI Therapy

Anastrozole was taken by 8 patients for a median duration of 16 months (range: 3–60 months), with 6 of those patients having received prior tamoxifen treatment. Of the 8 patients, 3 were treated in the adjuvant setting and 5 in the metastatic setting. The duration of treatment depended on clinical response. Toxicity from treatment was reported by 3 patients (37.5%), with 1 report each (12.5%) of decreased libido, leg swelling, and depression (Table IV). No patient discontinued anastrozole treatment because of toxicity.

Letrozole was prescribed for 5 patients in the metastatic setting after prior tamoxifen treatment. The median duration of letrozole treatment was 10 months (range: 10–27 months), with 3 patients receiving 10 months of therapy. Toxicity with letrozole was reported by 2 patients (40%). Both experienced peripheral edema, and 1 additionally reported hot flashes. No patient terminated letrozole treatment because of toxicity. The patient who experienced only peripheral edema with letrozole had developed a rash with tamoxifen treatment. The patient who experienced hot flashes and peripheral edema with letrozole also reported hot flashes with tamoxifen treatment.

4. DISCUSSION

Studies evaluating toxicity with tamoxifen in male breast cancer are extremely limited. To our knowledge only one study on the subject has been published [26]. In that study, 62.5% of men with breast cancer reported toxicity on tamoxifen treatment, with 20.8% discontinuing treatment because of side effects. The most commonly reported adverse effect was decreased libido in 29.2% of patients, followed by weight gain in 25% and hot flashes in 20.8%. Mood alterations, depression, pruritus, and venous thromboembolic events were also noted.

In the present retrospective study of men receiving endocrine therapy for breast cancer, we observed a similar rate of adverse effects from tamoxifen treatment (50%) and similar complaints (decreased

TABLE IV Reported toxicity to anastrozole treatment

Pt	*Treatment setting*	*Time on treatment (months)*	*Anastrozole toxicity*	*Prior tamoxifen treatment*	*Tamoxifen toxicity*
1	Metastatic	5	None	Yes	Pulmonary embolism
2	Adjuvant	46	Depression	Yes	Decreased libido, weight gain, rash
3	Adjuvant	60	Decreased libido	No	NA
4	Metastatic	12	None	Yes	None
5	Metastatic	3	None	Yes	None
6	Metastatic	6	None	Yes	None
7	Adjuvant	51	None	No	NA
8	Metastatic	20	Leg swelling	Yes	Erectile dysfunction

Pt = patient; NA = not applicable (no tamoxifen treatment).

libido, weight gain, hot flashes). In addition, we also observed cases of erectile dysfunction and rash in men with breast cancer treated with tamoxifen. Our treatment withdrawal rate of 23.7% was similar to the treatment withdrawal rate of 20.8% reported in the earlier study.

Compared with women receiving tamoxifen for breast cancer, men taking the drug experience comparable overall rates of toxicity, with perhaps fewer reports of hot flashes, but with similar rates of mood disturbance. The reports of decreased libido and of erectile dysfunction experienced by men treated with tamoxifen are interesting. It has been proposed that male sexual dysfunction with tamoxifen use is caused by decreased serum testosterone levels [25]. Future prospective studies evaluating the sexual dysfunction experienced by men taking endocrine therapy for breast cancer are needed.

In the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial, 61% of women with early-stage breast cancer treated with anastrozole reported 1 or more side effects, with 6% discontinuing treatment because of toxicity. The toxicity most commonly reported was hot flashes, in 35.7% of patients. Fatigue and mood disturbances were reported in 18.6% and 19.3% respectively [13,27]. In the metastatic setting, Buzdar *et al.* reported that 22% of women treated with anastrozole complain of hot flashes, 38% experience gastrointestinal disturbance, and 20% report nausea that may be related to the treatment dose [28]. In the present study, 8 men with breast cancer were treated with anastrozole (3 in the adjuvant and 5 in the metastatic setting), and 37.5% experienced toxicity of sufficient significance to be recorded in the patient's chart. Complaints included depression, decreased libido, and leg edema. Our sample size was too small to permit any definite conclusions to be drawn, but the results show that toxicity occurs in men with breast cancer treated with anastrozole and that the symptoms are similar to those seen with tamoxifen treatment, including decreased libido and mood alterations.

Although this retrospective study shows that endocrine treatments can produce adverse effects in men with breast cancer, it does have many recognized limitations. First, because of the relative rarity of male breast cancer, the sample size is small. Second, the data pertain to patients treated for both early and metastatic breast cancer. Patients with metastatic breast cancer may experience different symptoms because of their underlying disease rather than its treatment, which may lead to biased results. Third, the method of collecting the data relating to treatment toxicity may have influenced the results. Our study involved a retrospective chart review, and in light of the foregoing findings, the actual rate of toxicity from endocrine therapy in men with breast cancer may have been higher than that reported here.

5. CONCLUSIONS

In the current study, we demonstrated that endocrine therapy in male breast cancer is associated with toxicities similar to those reported in the female population. Men with breast cancer are just as likely to stop their prescribed endocrine therapy early as women with the disease are, thus potentially compromising the therapeutic benefit. Future prospective studies with larger datasets would help to substantiate the present findings. In addition, a better understanding of the toxicities experienced by male breast cancer patients using endocrine therapies would assist in the development of therapeutic strategies to improve compliance.

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