ORIGINAL ARTICLE

Mirtazapine for the Treatment of Hot Flushes in Breast Cancer Survivors: A Prospective Pilot Trial

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■ **Abstract:** The purposes of the study are to evaluate the efficacy and safety of mirtazapine 30 mg/daily for 12 weeks to reduce hot flushes (HF) in women with previous breast cancer and to assess the influence of the same treatment on sleep quality and other menopausal symptoms. A prospective pilot trial was conducted in 40 breast cancer patients with at least seven HF per day. A HF diary was completed daily; sleep quality and other menopausal symptoms were assessed with the Pittsburgh Sleep Quality Index (PSQI), the Menopause Rating Scale (MRS) and the SF-36 Health Survey. Treatment was never started by 13 out of 40 patients (32.5%) and was interrupted by 7 out of 27 patients (25%) due to of the occurrence of side effects (mostly somnolence). In the remaining 20 patients who completed the three months treatment period, there was a 55.6% ($p < 0.05$) reduction in HF frequency and 61.9% ($p < 0.05$) reduction in HF score as compared to baseline. A significant reduction in the MRS score (32.8%; $p < 0.05$) was observed. Mirtazapine appears to be effective in reducing HF in breast cancer survivors. The more frequent side effect was somnolence. A sizeable compiliance problem has been observed due to the reluctance to take antidepressant drugs and to side effects. ■

Key Words: breast cancer survivors, hot flushes, menopausal symptoms, mirtazapine

Hot flushes (HF) are one of the most prominent complaints reported by approximately 65% of breast cancer survivors (1). Other frequents complaints include depression, anxiety, sleeping difficulties, and sexual dysfunctions (2).

Estrogen and progestogens supplementation (HRT) is effective in reducing HF, but is considered contraindicated for patients with a history of hormone-dependent tumors (3). Recently, the prospective placebo-controlled HABITS trial (4) has been stopped because of a significant higher recurrence rate in patients who received estrogens. Progestogens alone, such as megestrol acetate (5,6) or medroxyprogesterone acetate (6) have been shown to be highly effective in relieving HF, but long-term safety in these women has not been demonstrated. Vitamin E (7) and isoflavones supplementation (8) have also been considered, but they are no more effective than placebo.

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Recently, attention has been focused on newer antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs). It has been demonstrated that a catabolic disorder of serotonin may be involved in the mechanism underlying HF (9) and several controlled clinical trials have shown that venlafaxine (10), fluoxetine (11), and paroxetine (12) are effective in controlling HF. A specific pharmacologic activity on the 5-HT (2A) receptor subtype may also play a key role in the occurrence of HF, as observed with mirtazapine (13,14), a different antidepressant drug belonging to the category of noradrenergic and selective serotoninergic antidepressants (NaSSAs). Also mirtazapine is a potent antagonist of noradrenergic receptors alpha 2 and this characteristic can contribute to its therapeutic effects. A case report on four subjects (14) has suggested that mirtazapine may be effective in women with severe HF associated with depressive symptoms. Recently, Perez et al. (15) showed that mirtazapine, at a dose ranging from 15 to 30 mg/day, reduced HF activity by 59% in 16 postmenopausal women, some of whom had been previously treated for breast cancer.

The aim of this pilot open-label study is to determine the efficacy on HF and the tolerability of a standard dose of mirtazapine (30 mg/day) in women with a history of breast cancer; the secondary end point is to evaluate the quality of sleep and some other aspects of the quality of life, possibly related to breast cancer diagnosis and premature menopause.

MATERIALS AND METHODS

Forty consecutive women attending the outpatient clinic for menopausal symptoms were enrolled in the study after giving written informed consent. All patients had suffered from breast cancer and had been operated at least 1 year before. Inclusion criteria were: physiologic or induced postmenopausal status (either amenorrhea for >12 months or amenorrhea for 6–12 months with a serum follicle-stimulating hormone (FSH) level greater than 40 mU/mL and estradiol less than 20 pg/mL, or bilateral oophorectomy or ovarian suppression by GnRH analogs) and the presence of troublesome HF (at least 7 per day), severe enough for the patients to seek therapeutic intervention.

Exclusion criteria were: use of any antidepressant treatment, progestogens or any other medication to treat HF within the previous 6 months; concomitant chemotherapy; uncontrolled hypertension (diastolic blood pressure >95 mmHg and/or systolic blood pressure >160 mm Hg); impaired renal or hepatic function; diabetes.

Any antiestrogen therapy (tamoxifen, aromatase inhibitors and GnRh analogs) was allowed provided that it was started at least 2 months before.

Before starting the treatment, each patient was asked to complete a HF diary for a week, reporting the number of the vasomotor events and their severity. A figure from 1 to 4 was attributed to each HF according to its severity; the score was calculated multiplying the total number of each mild, moderate, severe and very severe HF by the corresponding figures and summing up the four values. This questionnaire had been already validated in a series of previous trials (16). The HF diary was filled in during the next 12 weeks of treatment. At the end of each week, patients were asked to report any side effects.

Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), that is a validated instrument used to measure the quality and patterns of sleep in the adult (17). It differentiates "poor" from "good" sleep by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction over the last month.

The effect of treatment on overall menopausal symptoms was evaluated using the Menopause Rating Scale (MRS) (18) and the SF-36 Health Survey (19). The MRS is aimed at recording psychologic, somatovegetative, and urogenital symptoms; a composite score was obtained summing up the scores of these three specific aspects. The SF-36 Health Survey was conceived to analyze eight of the most important concept of health, four related to physical health and four to mental health component. For each concept of health, a score is calculated and then transformed into a global score ranging from 0 to 100 and expressed as a percentage; a global score ≥87.9 indicates excellent health, while a score ≤10.9 indicates poor health.

At baseline and at week 12 serum FSH, luteinizing hormone (LH), estradiol, complete blood count, vital signs, and weight were assessed.

Women enrolled in the study received mirtazapine at the dosage of 15 mg/day at bed time for the first week, increased to 30 mg/day during the following 11 weeks of treatment.

STATISTICAL CONSIDERATION

The primary end point of this study was to compare HF frequency and score after 4, 8, and 12 weeks of treatment with the basal value. The sample size was calculated under the assumptions of the detection of a 50% reduction in HF frequency, with 80% power at a two-sided alpha level of 0.05. These assumptions using a dependent-samples *t*-test required at least 20 evaluable patients. The dependent-samples *t*-test was used to analyze data and the Shapiro-Wilk test to confirm that the sample origins from a normal population. When normality of data was not confirmed the Wilcoxon signed-rank test was used.

Secondary outcome measures included the change occurring since baseline to 4 and 12 weeks of treatment of the MRS total score, PSQI total score and SF-36 Health Survey subscale scores.

SPSS software was used for statistical analysis. Statistical significance was determined by using an alpha level of 0.05 and two-sided tests.

RESULTS

Between January 2005 and June 2005, 40 women were enrolled in the study. Thirteen (32.5%) had

withdrawn from study after signing the informed consent and recording basal data and never began therapy; the reasons more frequently reported were the reluctance to assume antidepressant drugs or the fear that this drug may adversely affect cognitive function or cause side effects.

Of the remaining 27 women who started the treatment, 4 (14%) stopped after 2 weeks because of troublesome side effects, mostly somnolence and dizziness (n = 2), increased appetite and weight gain (n = 2) and are excluded from results evaluation; three other women (11%) dropped out after 1 month for somnolence (n = 3) and dizziness (n = 1).

Baseline characteristics of the women enrolled in the study are listed in Table 1. Mean age is 50 years (range 32–76 years) and 55% were younger than 50 years. More than half the patients (57.5%) underwent premature iatrogenic menopause because of the chemotherapy or ovarian suppression by GnRH analogs; almost 75% of all patients were taking hormonal adjuvant therapy. The mean daily frequency of HF was 10 and no patient had <7 HF per day; the duration of vasomotor symptoms was longer than 9 months in 57.5% of the cases.

Data on 1 month of therapy are available for 23 women; 20 patients have completed the study. After the first 4 weeks of treatment, there was a significant decrease of vasomotor symptoms as compared to baseline values; the mean decrease in weekly HF frequency was 46.9% ($p < 0.05$) and the mean reduction of weekly HF score was 49% ($p < 0.05$). The benefit increased after 8 weeks of mirtazapine, when the mean decrease in HF number and score was respectively of 56.5% ($p < 0.05$) and of 62.14% ($p < 0.05$); the effect remained stable during the last month of therapy (Figs 1 and 2). Tables 2 and 3 show the distribution of patients whose HF activity decreased by varying amounts over the treatment period. After the first month of therapy, 43.4% of the patients experienced a reduction in HF frequency ranging from 25% to 50% and 34.7% of them a decrease greater than 50% as compared to basal values. Over the next 4 weeks of treatment, 75% of women reported a reduction greater than 50% in the number of HF; no

Table 1. Patient Baseline Characteristics

Variable	N (%)
Age 32–50 years	22 (55)
Age >50 years	18 (45)
Iatrogenic menopause	23 (57.5)
Physiologic menopause	12 (30)
Surgical menopause	5 (12.5)
Tamoxifen or other antiestrogenic therapy	30 (75)
Hot flushes duration (>9 months)	23 (57.5)
Daily hot flushes frequency (mean)	10
Weekly hot flushes frequency (mean)	69.6
Weekly hot flushes score (mean)	194
Serum follicle-stimulating hormone (mIU/mL) (mean)	69
Serum estrogen (pg/mL) (mean)	10
Serum luteinizing hormone (mIU/mL) (mean)	34

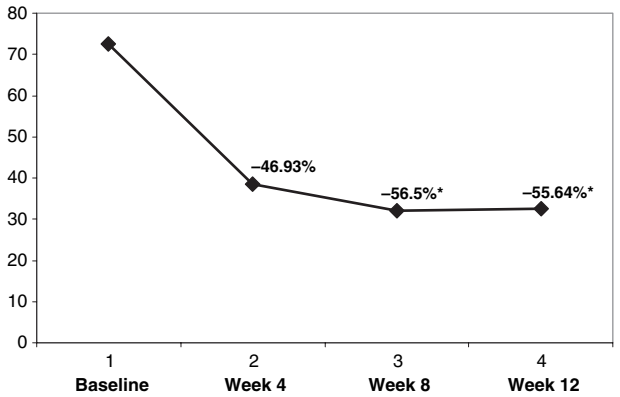

Figure 1. Mean hot flushes frequency reduction at 4, 8 and 12 weeks (*calculated on 20 patients).

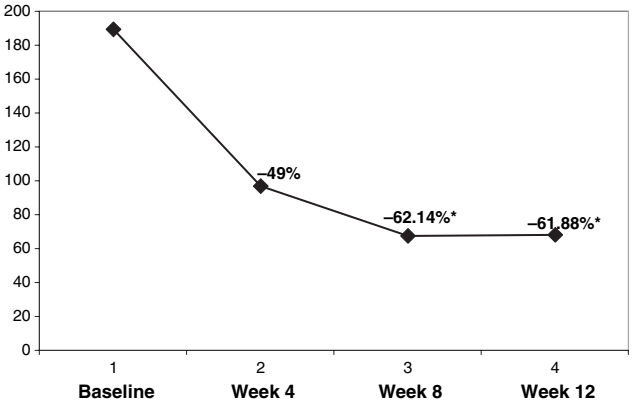

Figure 2. Mean hot flushes score reduction at 4, 8 and 12 weeks (* calculated on 20 patients).

Table 2. Reduction of Hot Flushes Frequency at 4, 8, and 12 weeks

	Hot flushes frequency		
	At week 4 (23 pts) (%)	At week 8 (20 pts) (%)	At week 12 (20 pts) (%)
<25% reduction	5 (21.7)	2 (10)	2 (10)
25–50% reduction	10 (43.4)	3 (15)	5 (25)
>50% reduction	8 (34.7)	15 (75)	13 (65)

Values in parenthesis are percentage. Pts, patients.

Table 3. Reduction of Hot Flushes Score at 4, 8 and 12 weeks

	Hot flushes score		
	At week 4 (23 pts) (%)	At week 8 (20 pts) (%)	At week 12 (20 pts) (%)
<25% reduction	3 (13)	3 (15)	3 (15)
25% – 50% reduction	8 (34.7)	2 (10)	3 (15)
>50% reduction	12 (52.1)	15 (75)	14 (70)

Values in parenthesis are percentage. Pts, patients.

further benefit was obtained after the third month of treatment. Similar data were obtained for the HF score.

The effect of mirtazapine 30 mg/day on the quality of sleep was favorable, but modest; the decrease in PSQI score at the end of therapy was 23.7% ($p = 0.11$). Somato-vegetative and psychologic symptoms, measured by the MRS, were improved, with a significant score reduction of 32.8% ($p < 0.05$) after 3 months of treatment as compared to basal values. Global SF-36 Health Survey Score did not show any significant change, neither in the mental, nor in the physical components (Table 4).

Table 4. PSQI, MRS, SF-36 Health Survey Score

Pittsburg Sleep Quality Index Score (PSQI)	Baseline (23 pts)	9.73
	At week 4 (23 pts)	8.27
	Reduction	15%
	p-value	0.16
	At week 12 (20 pts)	7.25
	Reduction	23.7%
	p-value	0.11
Menopause Rating Scale Score (MRS)	Baseline (23 pts)	22.47
	At week 4 (23 pts)	19.53
	Reduction	13.1%
	p-value	<0.05
	At week 12 (20 pts)	14.17
	Reduction	32.8%
	p-value	<0.05
SF-36 Health Survey Mental Component (%)	Baseline (23 pts)	57.91
	At week 4 (23 pts)	59.43
	Improvement	2.6%
	p-value	0.63
	At week 12 (20 pts)	60.4
	Improvement	2.1%
	p-value	0.75
SF-36 Health Survey Physical Component (%)	Baseline (23 pts)	59
	At week 4 (23 pts)	61.5
	Improvement	4.2%
	p-value	0.42
	At week 12 (20 pts)	60.2
	Improvement	0%
	p-value	0.88

Pts, patients.

DISCUSSION

Vasomotor symptoms are a relevant issue since they impair the quality of life of many women treated for breast cancer (1,2,20). This pilot study suggests that mirtazapine may be effective in reducing frequency and severity of HF in breast cancer survivors.

The pathophysiology of HF and the precise antidepressant mechanism of action on climacteric symptoms remain unknown (21). Mirtazapine acts as an antagonist on central presynaptic (alpha 2) adrenergic inhibitory receptors; this action results in an increase of central noradrenergic and serotoninergic activity. Mirtazapine is a potent antagonist of 5-HT2, 5-HT3 and histamine receptors and this may explain its prominent sedative effect. It is a moderate peripheral (alpha 1) adrenergic antagonist and this may produce occasional orthostatic hypotension. It is also a moderate antagonist at muscarinic receptors and this may explain the relatively low incidence of anticholinergic side effects associated with its use (22).

There are preliminary data in the literature on the use of mirtazapine at different doses (15–30 mg/day) for the relief of HF in postmenopausal women (14,15). In our study, we tested mirtazapine at the dosage of 30 mg per day for 12 weeks in breast cancer survivors, the majority of whom was also receiving tamoxifen and/or GnRH analogs or aromatase inhibitors. We decided to use the full dose of 30 mg per day because the sedative effect of mirtazapine is more pronounced using lower dosages and this side effect is the main reason for dropouts. In a previous trial, somnolence was reported in 54% of the patients treated with mirtazapine and this was the reason for discontinuing treatment in 10.4% of cases, while the second adverse effect was ''increased appetite/weight gain'' (8%) (22).

In our study, seven patients stopped treatment because of the onset of these side effects during the first month of treatment; the symptoms appeared during the first few weeks of therapy, but they largely disappeared over the following weeks in those who carried on the treatment.

In our study, the first adverse effect was ''somnolence'' (18%) and the second, that conditioned the discontinuation in the assumption of the treatment, was ''increased appetite/weight gain'' (7.4%). Also in the pilot study by Perez and Loprinzi et al. (15) using mirtazapine 30 mg/day for the relief of vasomotor symptoms increased appetite was reported during 4 weeks of therapy.

Patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance. It is unclear whether or not tolerance develops to the somnolent effects of the drug (22).

In our experience, the major problem with the compliance of mirtazapine was the unexpected reluctance to its use for indications other than depression. Actually, a relevant percentage of the patients enrolled did not start the treatment even though HF were a troublesome problem. The most frequent motivations were: fear of cognitive functions impairing, reluctance to receive other drugs besides to those required for adjuvant therapy and, in few cases, the contrary advice of the family doctor.

The efficacy of mirtazapine for the relief of vasomotor symptoms appears to be substantial, with a rapid decrease of HF frequency of about 56.5% and a further reduction after 2 months; continuing therapy for other 4 weeks did not change the number of HF.

The effect of mirtazapine on HF appears to be superior to the benefit obtained with a placebo; in fact, all double-blind placebo-controlled trials in breast cancer survivors have shown that placebo obtains a reduction of HF ranging from 25 to 35% (10–12).

Concerning sleep quality, the 23.7% reduction of the PSQI obtained at the end of treatment does not reach statistically significance. However, the subjective perception of women on treatment is suggestive for a beneficial effect, probably because the baseline score of 9.73 indicates a very poor sleep quality and even a small improvement is perceived as a fairly good benefit.

The menopausal symptoms evaluated using the MRS showed a significant improvement (score reduction 32.8%) after 12 weeks of mirtazapine use. On the contrary, the SF –36 Health Survey did not show a significant change; this may be because of the fact that either the mental and the physical components were estimated already good at the baseline week.

Finally, recent data (23) have suggested that several antidepressant drugs belonging to the class of SSRIs might interfere with tamoxifen metabolism, by inhibiting the CYP2D6 enzyme. This enzyme plays a role in the catalysis of tamoxifen to 4-hydroxy-*N*-desmethyl tamoxifen, a metabolite 100-fold more potent than tamoxifen. Although the clinical implication of this effect is unclear, it is important to consider that the newer antidepressants have different levels of CYP2D6 inhibition. In vitro studies have demonstrated that fluoxetine and paroxetine are potent inhibitors of this enzymes, whereas venlafaxine has weaker effect and mirtazapine does not inhibit CYP2D6 (24).

CONCLUSIONS

Mirtazapine at the dosage of 30 mg per day may be effective for the treatment of HF in breast cancer survivors, with acceptable side effects. Data of our preliminary study need to be confirmed in a larger, blinded placebo-controlled trial, evaluating also the efficacy and tolerability profile of different dosages. Experimental data about the possible negative interaction between the antiproliferative effect of tamoxifen on the breast and mirtazapine are reassuring.

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