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Efficacy of a New Compound Containing Cimicifuga Racemosa on Menopausal Symptoms in Women with Breast Cancer

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Abstract

The Hormone Replacement Therapy (HRT) is the "first-line therapy" for women with moderate / severe menopausal symptoms (hot flashes, profuse sweating, insomnia, osteoporosis).

However, when the symptomatology is lighter or there are contraindications to HRT (breast disease, cardiovascular disease, thrombophilic diathesis, smoke, etc), woman can benefit from some preparations such as phytoestrogens and Cimicifuga racemosa. At present there are insufficient data regarding the efficacy and safety of phytoestrogens in women with breast cancer: because this tumour disease is hormone-dependent, phytoestrogens should be considered contraindicated in patients survived to the disease.

Our study assessed both the effectiveness of a new compound containing Cimicifuga racemosa, Agnus-Castus, Ginger, Hyaluronic acid and Zinc on the neurovegetative menopausal symptoms (hot flashes, profuse sweating, insomnia) and its safe use in patients with breast cancer.

The results have shown that this compound is an excellent alternative to estrogen treatment of menopausal neurovegetative symptoms, even for patients with breast cancer who cannot take HRT or phytoestrogens.

Keywords: Menopause; Cimicifuga; Breast cancer; Phytoestrogens

Introduction

Menopause is characterized by amenorrhea and hypoestrogenism, resulting in a set of symptoms that include metabolic and vasomotor abnormalities (hot flashes, night sweats), neuropsychic deviations (insomnia, changes in appetite, anxiety and depression, memory loss, difficulty in concentration), osteoporosis, reduced sexual desire, vaginal dryness and urinary symptoms [1].

Menopause is a period of increased vulnerability due to several aspects: biological effects associated to neuroendocrine abnormalities, and psychological factors considered being "responsive" to all the physical changes of the women.

These changes cause a significant deterioration in the women' quality of life.

The Hormone Replacement Therapy (HRT) is the "first-line therapy" for women with moderate / severe menopausal symptoms (hot flashes, profuse sweating, insomnia, osteoporosis).

However, when the symptomatology is lighter or there are contraindications to HRT (breast diseases, cardiovascular diseases, thrombophilic diathesis, smoke, etc), woman can benefit from some preparations containing phytoextracts.

Among these, phytoestrogens are the most widely prescribed substances.

At present there are insufficient data regarding the efficacy and safety of phytoestrogens in women with breast cancer: because this tumour disease is hormone-dependent, phytoestrogens should be considered contraindicated in patients survived to the disease [2,3].

Conversely, Cimicifuga racemosa (CR) binds to hypothalamic receptors for serotonin, which exert an action similar to the one that this neurotransmitter plays in countering the autonomic symptoms of postmenopausal women [4-6]. Indeed, it was used by the North American Indians to tackle a wide variety of women's health issues, including climacteric symptoms [7-9].

The aim of our study is to evaluate the effectiveness of a new compound containing Cimicifuga racemosa, Agnus-Castus, Ginger, Hyaluronic acid and Zinc on menopausal symptoms compared to placebo, and to demonstrate its safety in patients with breast cancer that, for this reason, could not benefit either from the Hormone Replacement Therapy (HRT) phytoestrogens treatment.

Materials and Methods

All the 100 patients enrolled in the study attended the "Gynaecological Endocrinology Outpatient Clinic" of the Institute of Obstetric and Gynecological Pathology ("Santo Bambino" Hospital, Catania) from May 2015 to April 2016, complaining of persistent hot flashes, profuse sweating and insomnia.

Patients' inclusion criteria were:

- Age >50 but <56 years old;
- Spontaneous menopause from 18 months (Serum FSH >40 mIU/ml and Estradiol <20 pg/ ml);

- Ethnicity: all the patients were Caucasian females of Sicilian ancestry. Thus, patients from Bangladesh, Japan, China, India, USA and Northern Europe were excluded;

- Patients not on any medications for any pathologies (hypertension, dyslipidemia or any other medical or psychiatric illness) for at least 3 months before study enrollment;

- History of breast cancer.

Particularly:

- 50 patients had undergone QUART protocol (Quadrantectomy Conservative surgery + Radiotherapy);

- 30 women had undergone QUART protocol and they were still taking tamoxifen;

- 20 patients were subjected to unilateral total mastectomy for recurrence of cancer.

According to a randomization table, patients were divided into two groups:

- Group A: 50 patients intook a compound containing 80 mg of Cimicifuga racemosa (CR) + 40 mg Agnus-Castus + 50 mg Ginger + 30 mg Hyaluronic acid + 12,5 mg Zinc (1 tablet daily continuously for 6 months);

- Group B: 50 women took a placebo pill (1 tablet daily continuously for 6 months).

All the patients underwent bilateral mammography and breast ultrasound before and after therapy. None of the patients had side effects and it has not been reported any dropout from the study. Therefore, the compliance was defined optimal for all the patients.

The modified Kupperman Index was used to evaluate the severity of autonomic signs, taking in consideration the most relevant 3 symptoms: flushes, profuse sweating and insomnia.

Symptoms were defined as follows:

- Mild (score 3-9);

- Moderate (score 10-14);

- Severe (score 15-21).

Moreover, the number and the daily intensity of hot flushes were also evaluated through a self-filled diary characterized by the following fields:

0 = absent;

1 = mild;

2 = moderate;

3 = severe;

4 = very severe.

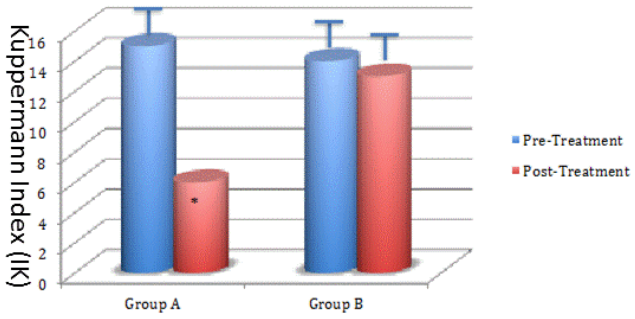
Results

Before therapy, Group A showed a mean Kupperman Index (IK) of 15 ± 2 and a "hot flashes degree" defined as "moderate-severe".

Group B had a mean IK of 14 ± 2 and a degree of "hot flushes" judged as "moderate". The statistical analysis of the results was performed using "chi-square" test.

After compound administration, the Group A showed a mean IK of 6 ± 1 and a "degree of hot flashes" defined as mild ($p < 0.05$).

No statistically significant reduction for any of the two parameters considered was found in the control group, after therapy: mean IK was 12 ± 2 and the degree of "hot flushes" was stably definable as "moderate" (Graph 1).



Graph 1: Kuppermann Index (IK) before and after treatment in Group A and B (* = $p<0.05$).

The Group A patients also demonstrated no pathological changes at mammographic and sonographic checks which had been performed after therapy with the compound.

Only one patient of Group B (who had undergone right breast QUART protocol about 6 years ago and actually not on tamoxifen therapy) reported, at mammogram, a "suspicious calcification of the right breast", turned out to an invasive lobular carcinoma recurrence. However, this case cannot be considered significant.

No patient reported side effects or adverse events.

Discussion

Menopause is a period of increased vulnerability due to several aspects: biological effects associated to neuroendocrine abnormalities, and psychological factors considered being "responsive" to all the physical changes of the women.

These changes cause a significant deterioration in the women' quality of life.

As previously reported, the Hormone Replacement Therapy (HRT) is the "first-line therapy" for women with moderate / severe menopausal symptoms (hot flashes, profuse sweating, insomnia, osteoporosis).

However, when the symptomatology is lighter or there are contraindications to HRT (breast diseases, cardiovascular diseases, thrombophilic diathesis, smoke, etc), woman can benefit from some preparations containing phytoextracts.

Among these, phytoestrogens are the most widely prescribed substances.

They are heterocyclic phenols and, despite not having a steroid structure, are similar to the 17-β-estradiol from both a functional and, in part, structural point of view; therefore, phytoestrogens compete for the same receptors of endogenous estrogens, by carrying out a weaker

estrogenic-like action: the most used phytoestrogens are soy isoflavones [1].

Several studies conducted in the Eastern countries show that the intake of large quantities of soybeans from childhood is associated with a reduced risk of breast cancer.

Indeed, testing on animals suggest that this is due to the differentiation of the mammary cells and to a decrease of the terminal buds that are the sites of early tumor proliferation [10,11].

However, nowadays there is no convincing evidence to suggest a protective efficacy of isoflavones on breast cancer if taken in adulthood and by the western populations [12-14].

Beginning the consumption of phytoestrogens and, in particular, of soy isoflavones during the perimenopausal period can cause the growth of a latent ER-positive breast cancer, while undertaking therapy with phytoestrogens five years after menopause probably induces cell death by apoptosis [15].

Indeed, in vitro studies have shown that genistein, equol and phytoalexins stimulate cell growth in MCF7: 5C (breast cancer cell line) after 3 days of low concentration estrogen deprivation (situation which mimics the perimenopausal status); these cells are adapted to a rich in estrogen environment and they grow through the natural estrogen supply provided by phytoestrogens.

Conversely, phytoestrogens, although less potent than estradiol, induce apoptosis in MCF7 cells that have undergone estrogen deprivation for a long time [15,16].

However, these mechanisms are not well known and require further studies.

The Cimicifuga Racemosa (CR) or Black Cohosh is a substance that was used by the Indians of North America to counter a wide variety of women's health issues, including climacteric symptoms [7,8,17].

Indeed, our protocol and all the studies in literature are based on this original species of CR that is from America, while the Asian Cimicifuga seems to have other features and, to date, clinical data on its use are not available [17,18].

The Black Cohosh is able to bind to hypothalamic receptors for serotonin, which exert an action similar to the one that this neurotransmitter plays in countering the autonomic symptoms of postmenopausal women [4-6]. Currently, the recommended dose should not exceed 80 mg daily [19].

Indeed, it was shown that the beneficial effects of CR on menopausal symptoms are not associated with systemic estrogen-agonists effects [20]: it was highlighted no evidence of any change in vaginal cytology, in E2, FSH, LH, prolactin and SHBG levels after treatment with CR [21,22].

Probably, the positive effect of Black Cohosh on hot flushes and other autonomic symptoms is due to its dopaminergic, adrenergic and serotonergic actions [17].

Recently, it has been demonstrated the presence of N-methyl-serotonin (a derivative of serotonin) and triterpenes (with GABA-ergic action) in various extracts of CR [23]: their synergistic action seems to improve the climacteric symptoms.

Black Cohosh seems to have a positive effect on bone remodelling and on trophism of the vaginal mucosa [24].

According to our results, other previous studies have shown that treatment with CR for 24 weeks is not only effective in improving of hot flashes, night sweats, insomnia, depression and headache, but it is also safe for patients with a personal history of estrogen-dependent malignant disease (breast and endometrium carcinoma) [25].

Indeed, Black Cohosh does not bind neither to α nor β receptors [26, 27], and it inhibits the proliferation of MCF-7 cells, that are the human breast cancer cell lines more responsive to the estrogenic action [28-30].

Moreover, the breast glandular tissue and the MCF-7 cells express the enzyme aromatase, which is able to increase the availability of estradiol in breast tissue, converting androgens into estrogens. This conversion is deeply inhibited by Cimicifuga racemosa's extract [31], enhancing the protective effect of CR on the mammary gland.

The positive effects of the compound tested is surely due not only to Cimicifuga, but also to Agnus castus, a phytocomplex containing glycosides and flavonoids [32]: its main active ingredient is agnuside, which increase the hypothalamic dopaminergic tone [33].

Literature had not been reported interaction with tamoxifen [34] nor adverse reactions, except for occasional gastrointestinal discomfort [9].

We can therefore assert that the extracts of Black Cohosh (in particular a compound containing Cimificuga racemosa, Agnus Castus, Ginger, Hyaluronic acid and Zinc) are an excellent alternative to estrogenic treatment of menopausal neurovegetative symptoms, even for patients with breast cancer who cannot take HRT or phytoestrogens, as well as supported by the "American College of Obstetrics and Gynecology" guidelines [9].

However, further studies should be conducted to confirm the efficacy and safety of these extracts.

Declaration of interest

The authors report no conflicts of interest.

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