

Prospective Observational Study: The Role of a Bergamot Based Nutraceutical in Dyslipidaemia and Arthralgia for Subjects Undergoing Aromatase Inhibitors Based Therapy

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Abstract

Introduction: The aromatase inhibitors (AIs) constitute hormonal therapy in post-menopausal women with ER+ breast carcinoma. The most common side effects of these medicines are arthralgia and dyslipidaemia. Given the increase of cardiovascular risk associated with dyslipidaemia (high levels of LDL-C and TG, low levels of HDL-C), the principal aim of the study is to describe the efficacy of a nutraceutical containing extract of bergamot and artichoke, phytosterols and vitamin C on the parameters of the lipid profile in women undergoing hormone therapy (TC, HDL-C, LDL-C, TG). The secondary aim is to evaluate the possible effect of the nutraceutical on arthralgia pain, given the anti-inflammatory properties of the active natural ingredients of the product. **Materials and Methods:** The study was carried out on a total of 41 female subjects who suffered from arthralgia from aromatase inhibitors and drug-induced dyslipidaemia. The subjects' levels of TC, LDL-C, HDL-C, TG, Homocysteine, and uric acid were tested upon enrollment (t0) and thereafter at 3 (t1) and 6 months (t2) of observation. The study lasted 12 months from enrollment to follow-up. Participants took 2 tablets daily of the supplement after dinner for 6 months. Participants did not take any other medicines with the exception of 250 mg of paracetamol twice daily if required. **Results:** Subjects showed a normalisation of their lipid profile, together with some relief from pain, measured using the VAS. The increase of HDL-C ($p < 0.001$) levels was of particular note. No side-effects relative to the use of this product were reported. **Conclusion:** The results obtained open new therapeutic scenarios for the use of nutraceuticals in cancer patients, and especially in subjects exposed to a multiple pharmaceutical treatments, as a possible adjuvant tool and as natural device to limit side effects to a minimum.

Keywords: Aromatase inhibitors; Breast cancer; Dyslipidaemia; Bergamot; Nutraceuticals; Dietary supplement

Introduction

Aromatase inhibitors (AIs) are drugs used in postmenopausal patients with estrogen-receptor-positive (ER+) breast cancer, which represent the majority of breast cancers. Estrogen is the main hormone involved in the development and growth of breast tumors and estrogen deprivation remains a key therapeutic approach.^[1]

The third-generation AIs (anastrozole, letrozole and exemestane) appear to be very well tolerated, with a remarkably low incidence of serious short-term adverse effects, reflecting the remarkable specificity of their action. The commonest of these effects are hot flashes, vaginal dryness, musculoskeletal pain and headache.^[2]

However, the risk of important long-term skeletal problems, including osteoporosis, may increase with the use of AIs. Approximately 25% of postmenopausal women on AIs report arthralgia, skeletal and muscle pain.^[3,4]

These symptoms are common reasons for patients on AIs to be subjected to a rheumatology examination.^[5] Concerning the effects on cardiovascular health, a substantial proportion of patients on AIs develop drug-induced dyslipidaemia.^[6]

Large-scale epidemiological studies have shown that high serum levels of total cholesterol (TC) and LDL-cholesterol (LDL-C) are important risk factors for the development of cardiovascular diseases (CVD), and that low serum levels of HDL-cholesterol (HDL-C) and hypertriglyceridemia (TG)

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are associated with increased coronary heart diseases (CHD), morbidity and mortality.^[7,8]

According to the Aifa (Italian Medicines Agency) note 13th, subjects with medication-induced dyslipidaemias should first try and manage their risk factors with diet and a healthy life style. They could receive a NHS prescription of hypolipidemic drugs, according to the specific category of cardiovascular risk of the subject, if their dyslipidaemia is not well controlled by diet and physical activity.

The latest ESC (European Society of Cardiology) Guidelines for the Management of Dyslipidaemias^[9] published on August 2016, for the first time indicate dietary supplements and functional foods (known as “nutraceuticals”) as useful tools, in association to diet and a healthy life style, for the management of cardiovascular risk factors like LDL-C and TG. These can be used either as alternatives or in addition to lipid-lowering drugs.

The use of nutraceuticals in medicine could be considered as part of the so called “Complementary and alternative medicine” (CAM).

CAM has been defined as “any diagnosis, treatment or prevention that complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual framework of medicine”.

A European Survey of 2005, published in *Annals of Oncology*, showed how the use of CAM has been increased among cancer patients in the last 15 years, with 35.9% using some form of CAM.^[10]

Herbal medicines and remedies are the most commonly used CAM therapies, together with homeopathy, vitamins/minerals, medicinal teas, spiritual therapies and relaxation techniques. Herbal medicine use tripled from use before diagnosis to use since diagnosis with cancer. CAM are used mostly to increase the body’s ability to fight cancer, to improve physical and emotional well-being but also to overcome common side effects of drug therapies for cancer, such as nausea and vomiting or pain.

Taking into account all these issues, this prospective observational study was made with the aim of deepening the knowledge about the use of nutraceuticals for the management of common side effects of drug therapies and, in particular, with the aim of collecting data on subjects taking a nutraceutical composed of bergamot, phytosterols, artichoke and vitamin C for the management of moderate, AIs-induced dyslipidaemias.

The first objective of this study was to describe the effects of the dietary supplement on the parameters of the lipid profile (TC, LDL-C, HDL-C, TG), the secondary objectives were to evaluate its tolerability as well as the possible effects on joint pain.

Materials and Methods

Patients

Patients were enrolled from the outpatient clinic of Orthopedy, Physiatry, Rheumatology and Vascular Medicine - Nuovo

Regina Margherita Hospital, Rome, Italy. The group of subjects observed has been chosen from patients on AIs therapy who went to the outpatient clinic to be submitted to a rheumatology visit. They all were postmenopausal women with breast cancer and their age ranged from 43 to 80 years.

Subjects observed had been diagnosed with arthralgia and showed that they developed a drug-induced dyslipidaemia. A drug induced dyslipidaemia had been diagnosed to each subject since blood analysis prior to the beginning of the AIs therapy didn’t show any sign of dyslipidaemia. An informed consent was obtained from each patient according to the European Legislation and the protocol of the study was previously submitted and approved by the Regional Ethical Committee.

In addition, the study protocol was performed according to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected an a priori approval by the institution’s human research committee.

Measurements

Patients on AIs therapy are usually submitted to clinical tests to assess the condition of the bones and the lipid profile, which include: homocysteine, uric acid, vitamin D, serum calcium, serum phosphorus, PHT, TC, LDL-C, HDL-C, TG.

Parameters of our interest are: TC, LDL-C, HDL-C, TG, uric acid, homocysteine.

Pain is measured by a VAS (visual analogue scale for pain) 0-100 (100 mm) scale, with a score of 0 indicating “no pain” and a score of 100 indicating the “worst imaginable pain”.

Treatments

All the patients have been given recommendations about following a healthy diet and doing at least 30 minutes of physical activity every day.

The group of subjects observed in this study had been prescribed from their physicians to take, once a day, two tablets of a dietary supplement composed of bergamot, artichoke, phytosterols and vitamin C (COLBER® - ESSERRE PHARMA SRL, Rome, Italy), for the management of dyslipidaemia.

The participants didn’t take any other medicines (opioids or nonsteroidal anti-inflammatory drugs-NSAIDS or cortisones) with the exception of 250 mg of paracetamol twice daily if required for pain relief.

Methods

Subjects who had started the intake of the nutraceutical for not more than 7 days from the enrollment visit were included.

According to clinical practice, patients were visited and submitted to clinical tests every 3 months.

We have been collecting data on each subject for a period of 6 months of dietary supplement intake.

Overall, the study lasted 12 months, including the enrollment and observation period.

Statistical analysis

Data were collected and analyzed using SPSS software (Statistical Package for Social Science).

Descriptive statistics were made out for numerical data by mean, standard deviation, standard error of the mean while they were done for categorical data by number and percent.

Analyses were done using the dependent sample T-test to compare baseline and post-treatment values of the group.

A confidence interval of 95% has been chosen and a level of statistical significance of $p < 0.05$ has been considered acceptable for all the tests.

Results

We collected data from 41 postmenopausal women on AIs therapy with arthralgia and drug-induced dyslipidaemia. The average age of the group was 59 years (+/- 12 SD).

Concerning the AIs therapy, 25 patients (61%) were on anastrozole therapy, 11 patients (27%) were on exemestane therapy and 5 (12%) were on letrozole therapy.

Mean values of lipid profile at the baseline and after 3 months (T1) and 6 months (T2) of observation are showed in Table 1.

Table 1: Lipid profile of subjects at baseline (T0) and after 3 months (T1) and 6 months (T2) (mean values-mg/100 ml (SD)).

	T0	T1	p-value	T2	p-value
TC	247 (6.1)	225 (5.4)	<0.05	210 (5.3)	<0.01
LDL-C	164 (6.4)	135 (5.0)	<0.05	116 (5.0)	<0.001
HDL-C	47 (7.0)	52 (6.8)	<0.05	61 (6.5)	<0.001
TG	183 (7.3)	172 (6.9)	<0.05	162 (6.8)	<0.01

TC: Total Cholesterol LDL-C: Low Density Lipoprotein Cholesterol
HDL-C: High Density Lipoprotein Cholesterol TG: Triglycerides

The observed subjects experienced a normalization of their lipid profile through a reduction of TC by 15%, LDL-C by 29%, TG by 11% together with an increase in HDL-C by 31% after 6 months.

A slight reduction in the VAS values has also been noticed. Mean values of the VAS at baseline and at T1 and T2 are showed in Table 2. Other blood values are listed in Table 3.

Table 2: Mean values (SD) of VAS at baseline (T0) and after 3 months (T1) and 6 months (T2).

	T0	T1	p-value	T2	p-value
VAS pain (0-100)	57 (6.9)	48 (5.4)	<0.05	44 (5.0)	<0.05

VAS: Visual Analogue Scale for Pain (100 mm)

Table 3: Homocysteine and Uric Acid values at baseline (T0) and after 3 months (T1) and 6 months (T2). Mean values (SD).

	T0	T1	p-value	T2	p-value
Homocysteine	14.8 (4.5)	13.9 (3.5)	n.s	13 (3.5)	n.s
Uric Acid	7.6 (4.3)	6.8 (4.0)	n.s	6.1 (4.0)	n.s

All the 41 subjects completed the 6 months period of supplement intake and no side effects relative to the use of the supplement were reported.

Discussion

The use of AIs in the treatment of hormone-dependent early breast cancer is well established, leading to a recommendation for their use as adjuvant therapy in postmenopausal women. AIs markedly suppress plasma estrogen levels in postmenopausal women by inhibiting or inactivating aromatase, the enzyme responsible for the synthesis of estrogens from androgenic substrates (specifically, the synthesis of estrone from the preferred substrates androstendione and estradiol from testosterone).^[11,12]

AIs are described as first-, second- and third- generation inhibitors, according to the chronological order of their clinical development, and as type I or type II inhibitors, according to their mechanism of action.

Type I inhibitors are steroidal analogues of androstendione and bind irreversibly to the same site on the aromatase molecule.

Type II inhibitors are nonsteroidal and bind reversibly to the heme group of the enzyme by way of a basic nitrogen atom.

The third-generation inhibitors, developed in the early 1990s, include the triazoles anastrozole (Arimidex®) and letrozole (Femara®) and the steroidal agent exemestane (Aromasin®).^[13]

These drugs are administered orally and the mean degree of inhibition at clinical doses is greater than 97%. They have been demonstrated to have an increased potency of inhibition and clinical efficacy than first- and second- generation inhibitors like aminoglutethimide or fadrozole.

AIs are used only in postmenopausal women, the use of these drugs in premenopausal women with breast cancer, who have normal ovarian function is contraindicated. Their use is also contraindicated in women with estrogen-receptor- negative and progesterone-receptor-negative cancer.^[14]

These drugs have a high safety profile and are well tolerated; however, they have some characteristic side effects mainly due to estrogen deprivation.

AIs have adverse effects on bone turnover with a reduction of bone mineral density and an increase in the rate of fragility fractures.^[15]

Estrogens have a protective effect on the lipid profile in human subjects, and high levels of HDL-C and low levels of LDL-C are associated with high estrogen levels.

Therefore, the reduction of estrogen levels which occurs during adjuvant therapy for breast cancer may lead to a more atherogenic lipid profile and increased CHD risk.^[16]

The rates of CHD in women after the menopause are 2 to 3

times those of premenopausal women of the same age and the dramatic decline in estrogen levels during the menopause is associated with unfavorable changes in lipid profile.^[17]

Data on lipid profile were not systematically collected in the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial; however, the prevalence of low grade hypercholesterolemia was reported to be 2.6 fold higher in patients receiving anastrozole than in those taking tamoxifen (ATAC Trialists' Group 2005).^[18]

Most studies on anastrozole in postmenopausal women with early breast cancer have shown beneficial increases in HDL-C and favorable decreases in TG, while variable effects on the levels of TC or LDL-C were described.^[19]

In the ITA (Italian Tamoxifen Anastrozole) Trial, the switching to anastrozole after 2–3 years of tamoxifen was also associated with an increased incidence of lipid metabolism disorders (9.3% vs 4.0%, $p = 0.04$) with respect to patients receiving 5 years of tamoxifen treatment.^[20]

With regard to letrozole, this agent caused a deterioration of lipid profile with an increase of atherogenic risk ratios TC/HDL-C and LDL-C/HDL-C in postmenopausal women with metastatic breast cancer previously treated with tamoxifen.^[21]

When dyslipidaemia of AIs patients is not well controlled by diet and life style, patients should start a pharmacological therapy. Statins are the first therapeutic choice, followed by ezetimibe for patients who don't tolerate them.

Considering that anastrozole is an inhibitor of CYP1A2, CYP3A4 and CYP2C8/9 and letrozole is a modest inhibitor of CYP2C19, if these drugs are associated to rosuvastatin, a reduced activation or a reduced metabolism of rosuvastatin could be experienced.^[22]

On the other hand, pravastatin is a weak inducer of CYP3A4 and it could lower the plasma levels of AIs.

In the recent years, the use of nutraceuticals for the management of dyslipidaemia has been increased both in healthy and cancer subjects. The reason why patients often choose alternative remedies as an adjuvant tool to manage their cardiovascular risk factors is the perception of safety that natural products give and the efficacy which is often guaranteed, while the choice is increasingly driven by the physician.

In this study we observed a group of postmenopausal women on AIs therapy with drug induced dyslipidaemia who took a nutraceutical composed of bergamot, artichoke, phytosterols and vitamin C for 6 months.

We described the blood values of lipid profile of subjects at baseline (enrollment, not more than 7 days from the beginning of the intake), at T1 (after 3 months) and at T2 (after 6 months). Moreover, we collected data on VAS measuring the pain of subjects.

We noticed a statistically significant reduction of TC, LDL-C and TG together with an increase of HDL-C. A statistically significant reduction of VAS values has also been detected. Nutraceuticals are defined as pharmaceutical-grade and standardized nutrient, regulated and registered as dietary supplements and food supplements.

In the recent years we have witnessed a dramatic increase of pre-clinical and clinical studies on natural substances, often included in nutraceutical formulations, for the management of cardiovascular risk factors.

The 2016 ESC Guidelines indicate some nutraceuticals as useful for the management of dyslipidaemias such as monacolin and red yeast rice, dietary fibre, soy protein, omega 3 fatty acids.

Among the nutraceuticals, phytosterols are mentioned in the ESC guidelines. They occur naturally in vegetable oils and in smaller amounts in vegetables, fresh fruits, chestnuts, grains and legumes.

Phytosterols compete with cholesterol for intestinal absorption, thereby modulating TC levels.^[23]

Experimental and epidemiological evidence suggests that dietary polyphenols, in particular flavonoids, may play a role in ameliorating atherosclerosis, due to a pleiotropic anti-oxidative and anti-inflammatory effect proposed as underlying mechanism.^[24]

In particular, Bergamot (*Citrus bergamia* Risso et Poiteau), an endemic plant growing in the Calabrian region of Southern Italy, has a unique profile and a high content of flavonoids and glycosides in its juice and albedo such as neoeriocitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin, poncirin.^[25,26]

Many studies on the properties of bergamot derivatives has been published in the last few years. The anti-infective potential of bergamot juice and essential oil has been described in a systematic review by Cirimi and colleagues.^[27]

Moreover, bergamot juice has been found to be rich in 3-hydroxy-3-methylglutaryl neohesperidosides of hesperetin (brutieridin) and naringenin (melitidin)^[28] which demonstrated their activity on inhibiting HMG-CoA reductase, both in animal models of diet-induced hyperlipidemia,^[29] and in patients suffering from hyperlipidemia, hyperglycemia and metabolic syndrome^[30] showing a clear effect on TC, LDL-C, HDL-C, TG and glucose blood levels.

In 2015 Giglio and colleagues published a review on the effects of bergamot on dyslipidemia, collecting and analysing preclinical and clinical data available at the time.^[31]

The anti-oxidant and lipid-lowering activity of phytochemical formulation including bergamot fruit extract and other phytoextracts has been described in an *in vitro* and clinical observational study performed on subjects with moderate dyslipidemia.^[32]

Recently, the activity of a nutraceutical composed of bergamot 200 mg, artichoke 80 mg, phytosterols 120 mg and vitamin C 20 mg added to simvastatin 20 mg/day has been evaluated in comparison to simvastatin 40 mg/day on patients suffering from ischemic heart disease who had not achieved the therapeutic target. This study showed that the association of the nutraceutical composed to statin therapy, given orally for 3 months, allowed the reduction of daily dose of simvastatin while achieving target lipid values, without side effects.^[33]

The activity of the nutraceutical above mentioned has been also recently described in a study performed on 80 subjects with metabolic syndrome undergoing a controlled diet.

Subjects who took 1 tablet per day of a nutraceutical composed of bergamot 200 mg, artichoke 80 mg, phytosterols 120 mg and vitamin C 20 mg, in addition to their controlled dietary regimen, showed significant results on the improvement of their lipid and glycemic profile. On the contrary, no significant results were found in subjects who only followed the dietary regimen, without taking the nutraceutical.^[34]

Conclusion

In this study we have noticed the real-life effect of the intake of a dietary supplement made of bergamot, artichoke, phytosterols and vitamin C on the lipid profile in subjects with breast cancer taking hormone therapy.

Results show statistically significant improvements in lipid profile of the subjects and no side effects reported. Moreover, all patients had good compliance with the intake of the supplement throughout the observation period.

Studies like this could be useful to support the use of nutraceuticals and suggest a possible alternative therapy for the management of some risk factors that could be corrected with diet, as a support to diet itself and to a healthy life style, when the use of a pharmaceutical therapy could be avoided.

Despite the results being interesting, however this study has some limits, mainly due to its design, which was performed as an observational one, to the limited number of subjects involved and to the lack of a group of control.

Anyway, more randomized controlled studies on nutraceuticals are auspicious in order to confirm their efficacy and safety on population.

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Conflict of Interest

All authors disclose that there was no conflict of interest. Costanza Riccioni is a member of the Scientific Department of Esserre Pharma srl.

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