Use of an alfa-lipoic, Methylsulfonylmethane, Boswellia serrata and Bromelain dietary supplement (OPERA®) for aromatase inhibitors-related arthralgia management (AIA): a prospective phase II trial (NCT04161833)

Isacco Desideri1,2 · Sara Lucidi2 · Giulio Francolini1 · Icro Meattini1,2 · Lucia Pia Ciccone2 · Viola Salvestrini2 · Marianna Valzano2 · Ilaria Morelli2,5 · Lucia Angelini2 · Vieri Scotti1 · Pierluigi Bonomo1 · Daniela Greto1 · Francesca Terziani3 · Carlotta Becherini1 · Luca Visani4 · Lorenzo Livi2

Received: 16 February 2022 / Accepted: 29 March 2022 / Published online: 6 June 2022 © The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract
Aromatase Inhibitors (AIs) are recommended for the adjuvant treatment of hormone receptor positive breast cancer in both high-risk pre-menopausal and post-menopausal population; arthralgia is the main cause of discontinuation of therapy and affects up to 25% of population on AI treatment. The objective of the study was to prospectively evaluate OPERA® (GAMFARMA srl, Milan, Italy), a new dietary supplement where α-Lipoic acid, Boswellia serrata, Methylsulfonylmethane and Bromelain are combined in a single hard-gelatin capsule to be taken once a day. Fifty-three patients with arthralgia (NCI-CTCAE v4.0 grade ≥ 1) occurring during AI therapy were enrolled. All patients received OPERA® from enrollment (T0) up to sixth months (T3). Patients’ AI-related arthralgia was evaluated every two months with VAS Scale, PRAI questionnaire, and CTCAE scale. Primary endpoint was the number of patients with symptom resolution (G0) at T3 if compared to T0, according to CTCAE and VAS scale. Secondary endpoints were decrease in arthralgia intensity measured with PRAI score at T3 compared to baseline, safety of OPERA® and rate of AI interruption. Treatment with OPERA® supplement was overall well tolerated; no relevant toxicities related to OPERA® intake were reported. Seven subjects (13.2%) were not included in the final analysis because of consent withdrawal. 46 participants were eligible for final analysis. According to CTCAE scale, 10 out of 46 patients reported symptoms resolution at 6-month follow-up from the time of enrollment T0 (p = 0.0009). According to VAS score, 5 patients reported complete resolution of symptoms at T3 if compared to baseline (p = 0.0222). Analysis of PRAI score showed a significant reduction in arthralgia-related pain perceived (p = 0.0001). OPERA® was able to reduce the intensity of arthralgia related to AI therapy. Randomized, double-blind studies are warranted to confirm the effectiveness of this dietary supplement.

Keywords Arthralgia · Breast cancer · Aromatase inhibitors · Dietary supplement · Quality of life
Introduction

Aromatase Inhibitors (AIs) are recommended for the adjuvant treatment of hormone estrogen receptor positive (ER+) breast cancer (BC) in the post-menopausal population and in high-risk pre-menopausal patients in association with LHRH analogues. Third generation aromatase inhibitors have been shown to significantly improve patients’ outcome [1–3]. Along with their well-known detrimental effect on bone-health, one of the most peculiar AI-related side effects is represented by arthralgia [4]. Arthralgia affects up to 25% of patients on AIs, inducing AI suspension in a significant proportion of patients [5]. As non-compliance and early discontinuation of the treatment leads to a poorer prognosis [3], this raised growing interest in its management. Treatment of arthralgia is generally based on the use of pharmacological, non-pharmacological, and complementary medicine intervention. Commonly used drugs comprise nonsteroidal anti-inflammatory drugs (NSAIDS), anticonvulsants, neuroleptics, and antidepressants (among which duloxetine plays an emerging role with best evidence in the management of AI-related arthralgia so far) [6–8, 24]. However, long term use of these medical aids is often associated with important side effects [9]. Alternatively, physical therapy intervention and acupuncture have shown some benefit [10–12].

OPERA® (GAMFARMA srl, Milan, Italy) is a new dietary supplement with a series of compound with a theoretical impact on osteoarthritis and inflammatory conditions.

To evaluate the efficacy of OPERA® for AI-related arthralgia management, a phase II, monocenter, self-controlled clinical trial was designed and carried out in our institution.

Methods

ER + early BC post-menopausal patients, 18 years or older, with a Karnofsky performance status (KPS) ≥ 70, reporting arthralgia of any grade (≥ G1) during adjuvant AI therapy were included in this phase II, monocenter, self-controlled prospective trial.

Exclusion criteria encompass concomitant rheumatological (rheumatoid arthritis, spondyloarthopathies, psoriatic arthritis, etc.) or endocrinological diseases (acromegaly, hemochromatosis, diabetes, etc.); renal insufficiency; alcohol abuse; G ≥ 3 or greater arthralgia before the start of adjuvant AIs and not related to endocrine treatment; all medical conditions that, according to the investigator, could potentially influence or overcomplicate symptoms interpretation (trauma, glucocorticoid withdrawal, hypertrophic osteoarthropathy, osteoarthritis, avascular necrosis, gout, systemic lupus erythematosus, septic arthritis, etc.).

Arthralgia was defined according to the National Cancer Institute-Common Toxicity Criteria for Adverse Event (NCI-CTCAE) v4.0 [13].

OPERA®, as mentioned above, is a new dietary supplement with a series of compound with a theoretical impact on osteoarthritis and inflammatory conditions [α-Lipoic acid (240 mg), Boswellia serrata (BS) (40 mg), Methylsulfonylmethane (MSM) (200 mg), and Bromelain (20 mg)] combined in a single hard-gelatin capsule.

The role of alpha lipoic acid lies in its antioxidant activity capable of neutralizing both oxidative reactions and reducing the resulting oxidized forms, the latter involved in the onset and worsening of pain. Boswellic acids hinder the action of an enzyme (such as 5-lipoxygenase and elastase) responsible to produce substances that facilitate inflammatory processes. Methylsulfonylmethane has a chondroprotective activity by stimulating the synthesis of articular cartilage. Bromelain is an anti-edema proteolytic enzyme. All these compounds are particularly effective in the treatment of localized inflammation of the soft tissues and are useful in the treatment of pain and inflammation of various tissues and in osteoarticular pain deriving from osteoarthritis and degenerative and inflammatory processes of cartilage.

OPERA® is made according to GMP EU “Good Manufacturing Practice Europe”, it was subjected to regular chemical-pharmaceutical controls and registered and notified to the Italian Ministry of Health.

All patients were required to take orally OPERA® one capsule of 12 mg once daily, preferably in the morning on an empty stomach as first line treatment in the management of AI-related arthralgia. Patients were required to continue their AI throughout the 6 months period and thereafter if tolerated. Patients were not allowed to take other medications or supplements to relieve their joint pain during this time. Physical activity was not contraindicated, but we did not report if it was regularly practiced.

Arthralgia was assessed at the enrollment visit and subsequently every two months up to the sixth month after enrollment, using the following items: 16-item Patient-Reported Arthralgia Inventory (PRAI) [5]. Italian version, Visual Analog pain Scale (VAS) [14] and NCI-CTCAE v4.04 [13]. Overall, clinical assessment was performed at baseline (T0) and at 2, 4, and 6 months (T1, T2, and T3, respectively). There are no known side effects for the use of the OPERA food supplement; therefore, we reported any disturbance that could be treatment-related and defined them according to NCI-CTCAE v4.0.

Primary endpoint was symptom resolution at T3 if compared to T0, measured with CTCAE and VAS scale.
Secondary endpoints were decrease in arthralgia intensity measured with PRAI score at T3 compared to baseline, safety of OPERA® and rate of AI interruption. Informed consent was obtained from all individual participants included in the study. Study design procedures were reviewed and approved by the local institutional ethics committee. Information about this phase II trial is available in the National Institute of Health site at http://www.clinicaltrials.gov (NCT04161833). Continuous variables were presented with descriptive statistics. The 95% confidence interval of the arithmetic median or of the percentage frequency were calculated for the variables of clinical-prognostic interest. Interruptions of treatment were calculated as a percentage. Only patients receiving complete follow-up (6 months of treatment) have been considered in the final analysis. All data were statistically analyzed using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Chi square test was used to test the difference in terms of arthralgia prevalence measured by CTCAE and VAS scale at baseline and last follow-up, after 6 months. Variations in terms of median PRAI score at 6 months were tested through Wilcoxon test. To detect a statistically significant decrease of arthralgia (standard 20% decrease assumed) with symptoms resolution at T3 if compared to baseline, a sample size of 46 was needed with a statistical power of 80% and a significance level of 0.05. Considering a dropout rate of 10%, 51 enrolled patients represented the final sample size.

Results

Between November 2018 and April 2019, 53 patients were recruited (Fig. 1). All patients provided written informed consent. Mean age was 59 years (43–82), presenting mostly with KPS 100 (75% of cases). Twenty-five patients (45.3%) previously received chemotherapy in either neoadjuvant or adjuvant settings. The 94.33% of these patients received a taxane-based regimen in combination either with anthracyclines and/or trastuzumab. No patients reported neuropathy at the end of chemotherapy according to CTCAE. Concerning adjuvant hormonal therapy, letrozole was prescribed in most cases (48 patients, 90.5%). Full patients and treatment characteristics are listed in Table 1. Arthralgia occurred within a mean time of 21 months since the start of AI treatment (range 2–52 months).

Seven subjects (13.2%) decided to end their participation in the study prematurely after the enrollment and withdrew their consent for personal reasons. Therefore, they were excluded from analysis, as it was not possible to analyze the PROMs related to this subset patients. Forty-six participants were eligible for final analysis. Treatment with OPERA® supplement was overall well tolerated by patients. No significant acute toxicity related to the intake of OPERA® was reported during the study period; only two patients (4.35%) reported a G1 gastralgia, with no discontinuation of tablets. After 24 weeks of OPERA® administration, a significant improvement in arthralgia was detected. G2 arthralgia according to CTCAE scale is clinically meaningful (moderate pain, instrumental ADL limitations) compared to G1 (light pain). According to CTCAE scale, at baseline T0, most patients had G1 (43%) and G2 arthralgia (54%) with one patient presenting with G3 arthralgia (2%). At 6-month follow-up T3, a significant reduction in G ≥ 1 arthralgia assessed with CTCAE (Fig. 2) was observed, with 57% presenting with G1 symptoms, 17% with G2 arthralgia and with 10 out of 46 patients (22%) reporting symptoms resolution if compared to T0 (p = 0.0009). According to VAS (Fig. 3), at T0 54% of population was categorized as VAS2, 37%...
VAS3 and 9% had VAS1 arthralgia. AT T3, 5 patients (11%) reported complete resolution of symptoms if compared to T0 ($p=0.0222$). Significant decrease in symptoms intensity was also detected with Patient-Reported Outcomes (PROMs) assessment, with a median PRAI score reduction from 4.5 at baseline (95%CI 3.22–5.22) to 1.96 (95%CI 1.18–3.63) at T3 ($p=0.0001$) (Fig. 4). Compliance to AI therapy was assessed during every scheduled visit and resulted in a 100% adherence at the time of study completion. No disease recurrence was reported at the end of study follow-up.

**Discussion**

Oncological outcomes have been radically improved in recent years and the important achievements obtained in BC field have led to a growing interest in long term side effects of any pharmaceutical intervention prescribed in this setting, especially in the context of ER+ BC, which represents the most common type of BC diagnosed [15]. Nowadays, AI hormonal therapy is the cornerstone for the adjuvant treatment of ER+ early breast cancer [1–3]. However, AI-related increase in musculoskeletal symptoms was reported in all major trials leading to their approval [5, 16, 17]. The set of disorders and musculoskeletal symptoms reported by patients on AI therapy is commonly defined as arthralgia, to distinguish the series of discomforts, unrelated to degenerative or inflammatory pathologies, from arthrosis or arthritis. The clinical presentation and the severity of the symptoms are quite variable; generally, the manifestation is symmetrical and bilateral, involving small joints; mainly it manifests itself upon awakening, inducing motility reduction and begins within two months from treatment start. However, a late presentation is not uncommon, even two

| Table 1 Patients’ characteristics |
|----------------------------------|
| Age, median (range)             | 59 years (43–82) |
| Smoking habit n° (%)            |                  |
| Current smoker                  | 3 patients (5.7%)|
| Ex-smoker                       | 5 patients (9.43%)|
| Never smoker                    | 29 patients (54.71%)|
| Unknown                         | 16 patients (30.2%)|
| BMI, median (range)             |                  |
| BMI <25                         | 20 patients (38%)|
| BMI 25 < x < 30                 | 22 patients (41%)|
| BMI > 30                        | 11 patients (21%)|
| KPS (%)                         |                  |
| KPS 100 (75%)                   |                  |
| KPS 70–100 (25%)                |                  |
| Neoadjuvant chemotherapy n° (%) | 3 (5.66%)        |
| Adjuvant chemotherapy           | 22 (94.33%)      |
| Chemotherapy schedules (% patients) |            |
| TC                              | 7 patients (13.20%)|
| EC + (H)T + H                   | 9 patients (16.98%)|
| FEC                             | 2 patients (3.77%)|
| CMF                            | 1 patient (1.89%)|
| (H)T + H                       | 6 patients (11.32%)|
| Type AIs therapy                | 53 patients (100%)|
| Letrozole                       | 48 patients (90.5%)|
| Exemestane                     | 5 patients (9.5%)|
| Stage                           |                  |
| Ia                              | 30 patients (56.60%)|
| Iia                             | 10 patients (18.87%)|
| IIb                             | 6 patients (11.32%)|
| IIIa                            | 5 patients (9.43%)|
| IIIb                            | 2 patients (3.77%)|

*BMI Body-mass Index, KPS Karnofsky Performance Status, TC Taxotere + Cyclophosphamide, EC Epirubicin + Cyclophosphamide, H Trastuzumab, FEC 5-Fluorouracile + Epirubicin + Cyclophosphamide, CMF Cyclophosphamide + Methotrexate + 5-Fluorouracile*

![Fig. 2 NCI-CTCAE arthralgia score assessment over 6 months. NCI-CTCAE National Cancer Institute-Common Toxicity Criteria for Adverse Event, G grade, T0 clinical assessment at baseline, T1 clinical assessment at 2 months, T2 clinical assessment at 4 months, T3 clinical assessment at 6 months](image_url)
years after the start of treatment [18]. Moreover, in some cases symptoms may become increasingly severe, representing a significant limitation for normal daily activities and finally leading to treatment discontinuation. Despite the high incidence rate, little is known about the etiopathogenesis of these symptoms; the low estrogenic levels could represent the triggering cause [19]. Several pharmacological and non-pharmacological methods aimed at reducing arthralgia and improving therapy adherence with AIs have been analyzed in recent years. Arthralgia is commonly treated using NSAIDs, paracetamol, and other analgesic drugs. However, no high-level evidence supports the use of these treatments, aside from some published cross-sectional surveys [20, 21].

Alternatively, a switch to another AI has been investigated in prospective trials [22]. In their study, Briot et al. switched 179 patients who had discontinued anastrozole due to arthralgia to letrozole after a one-month wash-out period. Improvement in arthralgia and in extended compliance to AI medication beyond 6 months was reported. Concerning other pharmacological interventions, Prednisolone have been tested with promising results in small patient cohorts [23]. Duloxetine, indeed, was also tested in a large, randomized phase III trial (SWOGS1202) by Henry et al. [24]. Treatment population, as in our experience, included 299 stage I–III post-menopausal patients in adjuvant endocrine therapy with AIs for early BC and was randomized in a 1:1 fashion to duloxetine or placebo for 13 weeks for treatment of muscular-skeletal symptoms. Primary endpoint was average joint pain through 12 weeks and in the results duloxetine proved superior to placebo in the management of AIMSS although related to more frequent low-grade toxicities. Based on this study, Henry and colleagues then analyzed the association between Body Mass Index (BMI) and response to Duloxetine in patients with AIMSS, showing that obese patients obtained more benefit from duloxetine [25]. Concerning non-pharmacological interventions, yoga and exercise have been tested in a series of retrospective and prospective experiences with favorable results; nonetheless small patient number and non-validated outcome measures were common in these published experiences [12, 26, 27]. Acupuncture has been tested in randomized clinical trials (RCTs) with mixed results, with only one trial showing a benefit of acupuncture versus sham procedure in arthralgia reduction [12, 28–32]. Among nutraceuticals, omega-3 fatty acids (O3-FAs) have been investigated due to their known beneficial effect in rheumatoid arthritis. In a study conducted by Hershman et al., 262 women were randomly assigned to receive either O3-FAs or placebo for 24 weeks. Compared with baseline, the mean observed Brief Pain Inventory–Short Form (BPI-SF) score decreased by 1.74 points at 12 weeks and 2.22 points at 24 weeks with O3-FAs and by 1.49 and 1.81 points, respectively, with placebo [33]. The authors concluded that no meaningful difference was appreciable between O3-FAs and placebo arm in terms of arthralgia reduction. Other nutraceuticals have also been tested in this setting. Notably, a single-arm study assessed the efficacy of a complementary medicine regime involving sodium selenite, lens culinaris lectin, and plant enzymes including Bromelain. One-hundred-twenty-nine patients receiving either tamoxifen or AIs were enrolled in this trial. Benefit with this regime evaluated with an unvalidated PROM was reported by the authors [34]. Our study represents one of the few prospective trials demonstrating significant benefit in terms of arthralgia resolution with validated objective and PROMs assessment in a single cohort of patients undergoing AIs adjuvant therapy. Of course, several limits should be acknowledged when referring to our study. In fact, limited sample size and heterogeneity of included patients could have influenced the results. Patients’ mean age was 59 years while incidence of arthralgia is higher in older
patients. We included only early BC post-menopausal patients without regarding high-risk pre-menopausal population.

Taxanes are notably associated with independent increase of the risk of developing joint pain [35–37]. In our study population we did not evaluate the impact of taxanes on arthralgia and on its management. In other experiences reported in literature, taxanes are significant predictors of pain and of low baseline quality of life, in addition to AIs [38, 39]. In Crew et al. experience [40] patients who received taxane chemotherapy were more than four times likely than other patients to have AI-related joint pain and stiffness. Also, in Beckwee’s work [41] one of the predictors for the development of AIA included taxane-based chemotherapy.

On the other hand, some studies report contrasting results about the impact of a taxane-based regimen on the development of AIA. According to Kellogg Cancer Center work, there is no statistical difference in the incidence of arthralgias in patients under AI treatment with a history of chemotherapy (including taxane therapy) compared to those who did not receive chemotherapy [42]. In the Chinese experience [43], taxane use is not associated with arthritis or carpal tunnel syndrome compared to other chemotherapy regimens. Also, Italian experience shows no difference in the incidence of arthralgia in patients on AIs who had received taxanes or anthracyclines [44].

Furthermore, it has not been assessed whether the reduction in pain symptoms was also associated with a significant improvement in terms of quality of life. Overall, OPERA® administration in symptomatic patients yielded a significant reduction in rate and severity of reported pain and osteoarticular symptoms according to CTCAE [13] and VAS [14], with a significant decrease in symptoms severity according to the PRAI scale.

One of the main reasons for scarce adherence to AI therapy is the onset of side effects like musculoskeletal symptoms. The assumption of OPERA® may represent a significant advantage in compliance to AIs, therefore leading to a more effective hormone therapy with subsequent better outcomes in disease control. The treatment was overall well tolerated, with no significant side effects. These findings further corroborate the promising results reported by our group in a previous experience, where OPERA® intake was shown to improve chemotherapy-induced peripheral neuropathy (CIPN) symptoms in a series of prospective patients previously exposed to neurotoxic chemotherapy [45].

Conclusion

In conclusion, our findings about OPERA® daily intake show promising results in the management of AI-induced arthralgia in the setting of post-menopausal patients. Randomized double-blind studies are warranted to confirm the effectiveness of this dietary supplement. Furthermore, it is necessary to investigate the impact of arthralgia reduction in terms of quality of life and compliance with AI treatment.

Acknowledgements None.

Funding None.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This trial was approved by the local institutional ethics committee.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

References

1. Cuzick J, Sestak I, Baum M, ATAC/LATTE investigators, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol. 2010;11:1135–41. https://doi.org/10.1016/S1470-2045(10)70257-6.

2. Regan MM, Neven P, Giobbie-Hurder A, et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1–98 randomised clinical trial at 8-1 years median follow-up. Lancet Oncol. 2011;12:1101–8. https://doi.org/10.1016/S1470-2045(11)70270-4.

3. Ingle JN, Tu D, Pater JL, et al. Duration of letrozole treatment and outcomes in the placebo-controlled NCIC CTG MA.17 extended adjuvant therapy trial. Breast Cancer Res Treat. 2006;99:295–300. https://doi.org/10.1007/s10549-006-9207-y.

4. Howell A, Cuzick J, Baum M, ATAC Trialists’ Group, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years adjuvant treatment for breast cancer. Lancet. 2005;365:60–2. https://doi.org/10.1016/S0140-6736(04)17666-6.

5. Liana DC, Kenneth AW, Benjamin RS, et al. Validity and reliability of the Patient-Reported Arthralgia Inventory: validation of a newly-developed survey instrument to measure arthralgia. Patient Relat Outcome Meas. 2015;6:205–14. https://doi.org/10.2147/PROM.S47997.

6. Hack CC, Haberle L, Brucker SY, et al. Complementary and alternative medicine and musculoskeletal pain in the first year of adjuvant aromatase inhibitor treatment in early breast cancer patients. Breast. 2020;50:11–8. https://doi.org/10.1016/j.breast.2019.12.017.

7. Presant CA, Bosserman L, Young T, et al. Aromatase inhibitor-associated arthralgia and/or bone pain: frequency and characterization in non-clinical trial patients. Clin Breast Cancer. 2007;7(10):775–8. https://doi.org/10.3816/CBC.2007.n.038.
8. Henry NL, Banerjee M, Whicha M, et al. Pilot study of duloxetine for treatment of aromatase inhibitor-associated musculoskeletal symptoms. Cancer. 2011;117(24):5469–75. https://doi.org/10.1002/jcc.26230.

9. Ware JEJ, Roberts K, Rickett K, et al. Management of aromatase inhibitor induced musculoskeletal symptoms in postmenopausal early Breast Cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017;111:66–80. https://doi.org/10.1016/j.critrevonc.2017.01.010.

10. Roberts KE, Rickett K, Feng S, et al. Exercise therapies for preventing or treating aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer. Cochrane Database Syst Rev. 2020;29:1. https://doi.org/10.1002/14651858.CD012988.pub2.

11. Jacobsen PB, Muchnick S, Marcus S, et al. Pilot study of iyengar yoga for management of aromatase inhibitor-associated arthralgia in women with breast cancer. Psycho Oncol. 2015;24:1578–80. https://doi.org/10.1002/pon.3756.

12. Crew KD, Capodice JL, Greenlee H, et al. Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer. J Clin Oncol. 2010;28:1154–60. https://doi.org/10.1002/jcco.20970.

13. National Cancer Institute-Common Toxicity Criteria for Adverse Event. v4.03, 2010. Available from: https://www.eortc.be/services/doc/ctcaev4_03_2010-06-14QuickReference_5x7.pdf. Accessed 12 March 2020

14. Hawker GA, Mian S, Kendzierska T, et al. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res. 2011;63:S240–52. https://doi.org/10.1002acr.20543.

15. Bodai BI, Tuso P. Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. Perm J. 2015;19(2):48–79. https://doi.org/10.7812/TTPP.14-241.

16. Goss PE, Ingle JN, Martin S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy for receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst. 2005;97(17):1262–71. https://doi.org/10.1093/jnci/dji250.

17. Coomes RC, Hall E, Gibson LJ, et al. A randomized trial of exercise and three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med. 2004;350(11):1081–92. https://doi.org/10.1056/NEJMoa040331.

18. Burstein HJ. Aromatase inhibitor-associated arthralgia syndrome. The Breast. 2007;16:223–34. https://doi.org/10.1016/j.breast.2007.01.011.

19. Niravath P. Aromatase inhibitor-induced arthralgia: a review. Ann Oncol. 2013;24(6):1443–9. https://doi.org/10.1093/annonc/mdt037.

20. Crew KD, Greenlee H, Capodice J, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol. 2007;25(25):3877–83. https://doi.org/10.1200/jco.2007.10.7573.

21. Lombard JM, Zdenkowski N, Wells K, et al. Aromatase inhibitor induced musculoskeletal syndrome: a significant problem with limited treatment options. Support Care Cancer. 2016;24:2139–46. https://doi.org/10.1007/s00520-015-3001-5.

22. Briot K, Tubiana-Hulin M, Bastit L, et al. Effect of a switch of aromatase inhibitors on musculoskeletal symptoms in postmenopausal women with hormone-receptor-positive breast cancer: the ATOLL (articular tolerance of letrozole) study. Breast Canc Res Treat. 2010;120:127–34. https://doi.org/10.1007/s10549-009-0692-7.

23. Kubo M, Onishi H, Kuroki S, et al. Short-term and low-dose prednisolone administration reduces aromatase inhibitor-induced arthralgia in patients with breast cancer. Anticancer Res. 2012;32(6):2331–6.

24. Henry NL, Unger JM, Schott A, et al. A randomized placebo controlled phase III study of duloxetine for treatment of aromatase inhibitor (AI)-associated musculoskeletal symptoms in women with early-stage breast cancer. J Clin Oncol. 2014;32(15):5. https://doi.org/10.1200/JCO.2017.74.6651.

25. Henry NL, Unger JM, Till C, Schott AF, et al. Association between body mass index and response to duloxetine for aromatase-inhibitor associated musculoskeletal symptoms in SWOG S1202. Cancer. 2019;125(12):2123–9. https://doi.org/10.1002/cncr.32024.

26. Roberts K, Rickett K, Greer R, et al. Management of aromatase inhibitor induced musculoskeletal symptoms in postmenopausal early Breast cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017;111:66–80. https://doi.org/10.1016/j.critrevonc.2017.01.010.

27. Hilditch JR, Lewis J, Peter A, et al. Menopause-specific quality of life questionnaire: development and psychometric properties. Maturitas. 1996;24:161–75. https://doi.org/10.1016/S0378-5122(96)82006-8.

28. Nahm N, Mee S, Marx G (2018) Efficacy of management strategies for aromatase inhibitor-induced arthralgia in breast cancer patients: a systematic review. Asia-Pac J Clin Oncol. 2018;14:374–82. https://doi.org/10.1111/ajco.12845.

29. Mao JJ, Xie SX, Farrar JT, et al. A randomised trial of electroacupuncture for arthralgia related to aromatase inhibitor use. Eur J Cancer. 2014;50(2):267–76. https://doi.org/10.1016/j.ejca.2013.09.022.

30. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. Ann Intern Med. 2002;136:374–83. https://doi.org/10.7326/0003-4819-136-5-200203050-00010.

31. Bao T, Cai L, Giles JT, et al. A dual-center randomized controlled double blind trial assessing the effect of acupuncture in reducing musculoskeletal symptoms in breast cancer patients taking aromatase inhibitors. Breast Cancer Res Treat. 2013;138(1):167–74. https://doi.org/10.1007/s10549-013-2427-z.

32. Oh B, Kimble B, Costa DS, et al. Acupuncture for treatment of arthralgia secondary to aromatase inhibitor therapy in women with early breast cancer: pilot study. Acupunct Med. 2013;31(3):264–71. https://doi.org/10.1177/0903915312010309.

33. Hershman DL, Unger JM, Crew KD, et al. Randomized multicenter placebo-controlled trial of omega-3 fatty acids for the control of aromatase inhibitor-induced musculoskeletal pain: SWOG S0927. J Clin Oncol. 2015;33(17):1910–7. https://doi.org/10.1200jco.2014.59.5595.

34. Uhlenbruck G, Van Leendert S, Schneider B, et al. Reduced side-effects of adjuvant hormone therapy in breast cancer patients by complementary medicine. In Vivo. 2010;24(5):799–802.

35. Fernandes R, Mazzarello S, Hutton B, Shorr R, Majeed H, Ibrahim MF, Jacobs C, Ong M, Clemons M. Taxane acute pain syndrome (TAPS) in patients receiving taxane-based chemotherapy for breast cancer: a systematic review. Support Care Cancer. 2016;24(8):2633–50. https://doi.org/10.1007/s10786-016-2325-5.

36. Salhi S, Fitzgerald B, Freedman OC, Amir E, Napolskikh J, Salvo N, Dranitsaris G, Clemons M. Incidence of taxane-induced pain and distress in patients receiving chemotherapy for early-stage breast cancer: a retrospective, outcomes-based survey. Curr Oncol. 2010;17(4):42–7. https://doi.org/10.3747/coc.17.4156.

37. Fernandes R, Mazzarello S, Joy AA, Pond GR, Hilton J, Ibrahim MFK, Canil C, Ong M, Stober C, Vandermeer L, Hutton B, da Costa M, Damaraju S, Clemons M. Taxane acute pain syndrome
(TAPS) in patients receiving chemotherapy for breast or prostate cancer: a prospective multi-center study. Support Care Cancer. 2018;26(9):3073–81. https://doi.org/10.1007/s00520-018-4161-x.

38. Fenlon D, Addington-Hall JM, O’Callaghan AC, Clough J, Nicholls P, Simmonds P. A survey of joint and muscle aches, pain, and stiffness comparing women with and without breast cancer. J Pain Symptom Manag. 2013;46(4):523–35. https://doi.org/10.1016/j.jpainsymman.2012.10.282.

39. Laroche F, Perrot S, Medkour T, Cottu PH, Pierga JY, Lotz JP, Beerblock K, Tournigand C, Chauvenet L, Bouhassira D, Coste J. Quality of life and impact of pain in women treated with aromatase inhibitors for breast cancer: A multicenter cohort study. PLoS ONE. 2017;12(11):e0187165. https://doi.org/10.1371/journal.pone.0187165.

40. Crew KD, Greenlee H, Capodice J, Raptis G, Brafman L, Fuentes D, Sierra A, Hershman DL. Prevalence of joint symptoms in post-menopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol. 2007;25(25):3877–83. https://doi.org/10.1200/JCO.2007.10.7573.

41. Beckwée D, Leysen L, Meuwis K, Adriaenssens N. Prevalence of aromatase inhibitor-induced arthralgia in breast cancer: a systematic review and meta-analysis. Support Care Cancer. 2017;25(5):1673–86. https://doi.org/10.1007/s00520-017-3613-z.

42. Menas P, Merkel D, Hui W, Lawton J, Harper A, Carro G. Incidence and management of arthralgias in breast cancer patients treated with aromatase inhibitors in an outpatient oncology clinic. J Oncol Pharm Pract. 2012;18(4):387–93. https://doi.org/10.1177/1078155211434853.

43. Chien HC, Kao Yang YH, Kwoh CK, Chalasani P, Wilson DL, Lo-Ciganic WH. Aromatase inhibitors and risk of arthritis and carpal tunnel syndrome among Taiwanese women with breast cancer: a nationwide claims data analysis. J Clin Med. 2020;9(2):566. https://doi.org/10.3390/jcm9020566.

44. Moscetti L, Agnese Fabbri M, Sperduti I, Fabrizio N, Frittelli P, Massari A, Pompei L, D’Auria G, Pofi E, Ruggeri EM. Adjuvant aromatase inhibitor therapy in early breast cancer: what factors lead patients to discontinue treatment? Tumori J. 2015;101(5):469–73. https://doi.org/10.5301/tj.5000376.

45. Desideri I, Francolini G, Becherini C, et al. Use of an alpha lipoic, methylsulfonylmethane and bromelain dietary supplement (Opera®) for chemotherapy-induced peripheral neuropathy management, a prospective study. Med Oncol. 2017;34(3):46. https://doi.org/10.1007/s12032-017-0907-4.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.