European Review for Medical and Pharmacological Sciences 2023; 27: 11643-11652

Oxygen-ozone autohemotherapy in breast cancer patients suffering from fatigue and musculoskeletal pain upon aromatase inhibitors treatment: a case-series study

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Abstract. – OBJECTIVE: In patients with breast cancer and positive hormone receptors, aromatase inhibitors are effective in reducing the risk of recurrences and are active in progressing the disease in this setting. On the other hand, fatigue and painful musculoskeletal side effects can significantly reduce treatment compliance. With no further treatment options to control these symptoms, non-pharmaceutical interventions, such as oxygen-ozone therapy, may play a role in managing rheumatologic symptomatology inasmuch. We have previously reported evidence on the effectiveness of oxygen-ozone in the treatment of pain and fatigue in chronic fatigue syndrome and fibromyalgia patients and in oncological patients as well.

PATIENTS AND METHODS: In this study, we reported 6 cases of patients (mean age 64 yrs, all Caucasian females) with breast cancer upon treatment with anastrozole (Arimidex®), suffering from musculoskeletal pain, weakness and fatigue, and therefore treated with oxygen-ozone major autohemotherapy according to the Italian Scientific Society of Oxygen Ozone Therapy (SIOOT) protocol. Pain was measured with a 10-item Numerical Rating Scale (NRS) and fatigue with a 7-item Fatigue Scoring Scale (FSS).

RESULTS: A reduction of at least 66% of pain (from 9.43 ±0.54 SD to 2.36 ±1.32 SD, $p<0.001$) and 66.26% of fatigue were obtained for all the cases.

Pain and fatigue disappeared within one month from ozone therapy, and a healthy painless state lasted for many months following the oxygen-ozone therapy.

CONCLUSIONS: The oxygen-ozone therapy is a sound opportunity for breast cancer patients to reduce anti-aromatase-induced pain, fatigue, and musculoskeletal symptoms.

Key Words:
Breast cancer, Ozone, Anti-aromatase, Ozone therapy, Pain, Fatigue

Introduction

Aromatase (CYP-19-A1) is an enzymatic system owing its name to the fact that transforms the A ring of steroids into an aromatic ring through the oxidation and elimination of a methyl group, so forming estrogens, which are involved in the development and malignancy of tumor cells[1]. The inhibition of estrogen production by aromatase inhibitors has been considered a treatment option for breast cancer[2-5]. However, aromatase inhibitors cause arthralgias and musculoskeletal symptoms in subjects with breast cancer during their therapy regimen[6,7].

This kind of adverse effects raises some issues about the need to use integrative oncology as an adjunct treatment to improve the final outcome of conventional therapy[8], even including aerobic exercise[9], as post-treated patients are affected by a considerable deal of symptoms, which could preclude a normal and comfortable daily social life[10].

Pharmaceuticals blocking the aromatase activity reduce the amount of estrogen in the circulation and, consequently, the number of hormones that can reach any residual tumor cells[11-13]. While the clinical efficacy of aromatase inhibitors is widely demonstrated, yet these too can have some adverse effects, as is the case with many drugs[14]. Joint pain and osteoporosis are among

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the most frequent and often severe effects, usually compelling physicians to plan and adopt targeted protocols for pain and fatigue relief[15-18]. Cancer-related fatigue, for example, is particularly concerning in the elderly and, in this scenario, integrative adjunct treatment enabled to address fatigue and discomfort would be of paramount importance[19,20].

Joint pain affects 20-50% of patients in different degrees from woman to woman; more often, painful symptoms are symmetrical (in the hands, wrists, knees) and appear from 2 to 10 months after therapy starting[16]. The underlying cause of pain has a multi-factorial pattern, although low levels of estrogens can promote an inflammatory state in the joints[16,21].

If the extent of pain is such that to affect the patient's quality of life, the first approach may be replacing the drug with another compound belonging to the same category[22]; otherwise, a rheumatological consultation will allow for a better evaluation of the causes of the pain and the prospects that may exist to control it with pharmacological and even non-pharmacological therapy[23]. The pharmacological approach should be sequential and suited to the intensity of the pain, as it is quantified with appropriate assessment scales. The drugs that can be used are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), analgesics, cortisones, and alongside the supporting function of vitamin D and C[24,25].

NSAIDs perform analgesic and anti-inflammatory activities. However, the response to these drugs is individual and varies from patient to patient, as well as different adverse effects[26].

Analgesics, on the other hand, are known to target pain and be pain relief pharmaceuticals, not necessarily targeting the inflammation response, and the choice of different drugs, such as opioids, varies according to the extent of pain (mild pain, non-opioid drugs; moderate pain, weak opioids; intense pain, major opioids). Cortisones must be prescribed carefully due to long-term side effects. Vitamin D is certainly important for bones, but the results regarding its effects on pain are somehow controversial[27].

On the other hand, integrative medicine and pharmacology may give fundamental insights to promote the use of other approaches in order to dampen the impact of anti-aromatase therapy-related adverse effects (pain, fatigue, and so on)[28-30].

In this perspective, ozone therapy can be a promising alternative. Ozone is an allotrope of oxygen, which has been widely used in recent reports to reduce musculoskeletal pain, discomfort, and fatigue, following cancer therapy, from an integrative-medical perspective[31-34]. The activity of medical ozone encompasses both an anti-inflammatory role and an anti-oxidant potential *via* the ozone-generated lipoperoxide known as 4-hydroxynonenal (4-HNE)[35] and its hormetic hallmark[36-38]. In accordance with previous studies[40-42], in our experience with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)[39], fibromyalgia and musculoskeletal pain and fatigue, we reported that the use of oxygen/ozone major autohemotherapy (O_2-O_3-MAHT) is able to reduce pain and fatigue and recover a good health status in the affected patients. Ozone exerts a beneficial activity on mitochondrial function and immune physiology, thus resulting as a hormetic modulator of the immune surveillance of complex painful pathologies[38,41,42].

In this case study, we investigated the use of O2-O3-MAHT to treat musculoskeletal pain and fatigue in six breast cancer patients undergoing therapy with aromatase inhibitors.

Patients and Methods

Patients

Outpatients referring to the Tirelli Clinical Group (Pordenone, Italy) joined the compliance with a standardized protocol of oxygen-ozone therapy from the Italian Society of Oxygen Ozone Therapy (SIOOT) and according to the Clinical Ethical Committee for ozone use (ISS Prot. 56/2020).

Eligible criteria for recruitment in this study were: a) previously diagnosed cancer treated with anti-aromatase inhibitors; b) presence of a symptomatic panel made by either weakness or pain or fatigue or a complex of these ones; c) expressing the willingness to undergo as outpatients one or more seats of major oxygen-ozone autohemotherapy (O_2-O_3-MAHT).

Exclusion criteria: a) patients with similar symptomatic patterns not related to previously diagnosed cancer; b) patients with similar symptomatic patterns not related to previously treated cancer with anti-aromatase inhibitors. The number of patients enrolled in the study was 13 (Caucasian patients, age range 63.07 ±6.41 SD, 84.6% females, Body Mass Index (BMI) ≤ 28.45 ±3.56). The final selection of six case reports (2 metastatic and 4 adjuvant) was performed by two independent authors of the study (MP and

CC). Cohen k was 0.4136 with a moderate agreement (71.43%). Each patient signed an informed consent for the study research and use of data, in compliance with the Declaration of Helsinki. Table I summarizes patients' features.

Oxygen-Ozone Major Autohemotherapy (O_2-O_3-MAHT)

The O_2-O_3-MAHT followed the SIOOT protocol for ozone therapy[38,43]. Each patient was subjected to at least two weekly sessions of O_2-O_3-MAHT; any treatment lasted 30-45 minutes for each session, leaving the subject able to come back to his/her own daily activities following the ozone treatment. A volume of 200 ml of venipuncture peripheral blood was collected in a European Community (CE) certified SANO3 collection bag and subjected to 45-50 μg/ml of ozone in a 5% O_2-O_3 mixture, continuously monitored and dosage modulated by UV-spectrometry in a Multiossigen® Medical 95 CPS device (Gorle BG, Italy). The instrumentation was enabled to work in the form of an outpatient unit for O_2-O_3 therapy and allowed physicians standing close to the patient's bed to customize the gas mixture according to the therapy request. In this perspective, the O_2-O_3 mixture generator was regulated by a proper microprocessor, ensuring the ozone delivery with the highest precision requested once the O_2-O_3 gaseous mixture and ozone amount were selected by the operator. A median of 204 mL, CI_{95} = 198-215 mL of blood was ozonized and reintroduced for each treated patient. Each patient was monitored up to 30 days following the second O_2-O_3-AHT session and asked to complete the questionnaires.

Pain and Fatigue Evaluation

The pain was evaluated by the Numerical Rating Scale (NRS-11) according to Hartrick et al[44], and other authors, then statistically evaluated[44,45]. Fatigue was evaluated with a 9-item Fatigue Severity Scale (FSS)[46] and data was statistically elaborated. Questionnaires were proposed in the interview form at the beginning of the O_2-O_3-MAHT and the following two weeks from the second session of ozone therapy.

Statistical Analysis

Values as mean ± SD (standard deviation) were evaluated with a non-parametric Kolmogorov-Smirnov test for $p < 0.05$. Score data were evaluated with the Kruskall-Wallis (KW) test for $p<0.05$. Data were analyzed with a SPSS v 24 software (IBM Corp., Armonk, NY, USA).

Logistic regression was applied to evaluate the success of the O_2-O_3-MAHT in the case reports, using the model:

$$p = \frac{1}{1 + e^{-(\beta_0 + \beta_{1x1})}}$$

for $p<0.05$

Table I. Patients' features upon the study admission.

Case #1	Age: 54	Chemotherapy: 3 cycles AC (60-600 mg/m^2) + 3 cycles Pxt (80-300 mg/m^2) Adjuvant therapy: Ana 20 mg/d	Diagnosis/Surgery: invasive mammary carcinoma, mastectomy	Symptoms: myalgia, muscle spasms, fatigue, insomnia
Case #2	Age: 62	Adjuvant therapy: Ana 20 mg/d for 6 months	Diagnosis/Surgery: Grade 3-breast carcinoma, quadractectomy, local radiotherapy	Symptoms: arthralgia, musculoskeletal pain and weakness with fatigue
Case #3	Age: 56	Adjuvant therapy: Ana 20 mg/d for 4 months	Diagnosis/Surgery: Grade 2-breast carcinoma, mastectomy, local radiotherapy	Symptoms: spasms, musculoskeletal pain, fatigue
Case #4	Age: 69	Adjuvant therapy: Ana 20 mg/d for 3 months	Diagnosis/Surgery: Grade 3-breast carcinoma, mastectomy and radiotherapy	Symptoms: general weakness, fatigue
Case #5	Age: 72	Adjuvant therapy: Ana 20 mg/d for 3 months	Diagnosis/Surgery: Grade 3-breast carcinoma, surgically removed, with lung metastasis	Symptoms: general weakness, fatigue, severe musculoskeletal pain
Case #6	Age: 72	Adjuvant therapy: Ana 20 mg/d for 5 months	Diagnosis/Surgery: Grade 2-breast carcinoma	Symptoms: severe musculoskeletal pain

Results

Case #1

The first case concerns a 54-years old female patient in post-menopausal stage previously diagnosed with a high-grade, estrogen-receptor positive invasive mammary carcinoma, who was treated with a modified radical mastectomy. Initially, she underwent adjuvant chemotherapy consisting of four cycles of adriamycin/cyclophosphamide (AC) (60-600 mg/m^2) every three weeks followed by four cycles of Paclitaxel (Pxt) 80/300 mg/m^2. This therapy protocol was initially well tolerated, apart for rare episodes of myalgia and general weakness, rapidly resolved upon a reduction in the Pxt dosage. At the AC/Pxt therapy completion, the patient underwent the adjuvant treatment with Anastrozole (Ana) 20 mg/day in a single daily dose. Upon anastrozole (Arimidex®) therapy, two days later, the patient started to experience excruciating muscle spasms, fatigue, insomnia, and general weakness. Before starting the oxygen-ozone treatment, in the NRS-11 pain scale, the patient reported a mean value of 9.43 ±0.79 SD (for 7 days) and 9.71 ±0.49 SD for the next 21 days. Fatigue, evaluated by the 9-item, 7-point FSS scale, was 6.72 ±0.65 SD.

Over time, the patient increased the severity of their painful symptoms, so tried to address the same with *per os* analgesic drugs intake, without success. In June 2018, she resorted to our Clinical Service, i.e., to the Unit of Oncology and Oxygen-Ozone Therapy at the Tirelli Clinical Group, in Pordenone (Italy), to undergo oxygen-ozone therapy, after having approved our informed consent and ethical guidelines (in compliance with the Declaration of Helsinki).

The patient underwent twice a week four sessions of major oxygen-ozone autohemotherapy (O_2-O_3-MAHT) according to the protocol previously assessed by the Italian Society of Oxygen-Ozone Therapy (SIOOT) for other painful, discomfort, and fatigue symptoms[38-40,43].

Following the first two sessions, the patient was interviewed (on the third day following O_2-O_3-MAHT) for NRS scoring for three follow-up points: a) immediately after the first two O_2-O_3-MAHT (three days after); b) at the end of the whole therapy process; c) one month later. The respective values were: a) 8.28 ±1.11 SD (-12%, p = 0.06392, at the KW test); b) 3.42 ±1.40 SD (-63.64%, p = 0.00175, KW test); c) 2.14 ±0.90 SD (-77.3%, p = 0.00177, KW test). Fatigue, at the end of the O_2-O_3-MAHT, dropped down to 1.91 ±0.83 SD (-71.62%, p = 0.0007, KW test). The patient did not report any pain or fatigue symptoms in the last two years. We reported that O_2-O_3-MAHT reduced pain symptoms by about 80%. Fatigue symptomatology was not reported completely.

Case #2

A similar successful outcome was also observed for a 62-years old female patient in post-menopausal stage previously diagnosed with a bone metastatic disease of high-grade (grade 3), showing an estrogen-receptor positive invasive breast carcinoma, for which the patient was treated with a quadrantectomy and local radiotherapy. In September 2018, the patient started a therapy protocol with 20 mg/ml anastrozole (Arimidex®) (a dose/day) for six months. However, following three months of therapy (precisely 94 days), she reported arthralgia, musculoskeletal pain, and weakness with fatigue, and was counseled to refer to our clinical healthcare service to evaluate the possibility of an O_2-O_3-MAHT, for which we evaluated promising outcome. The patient was interviewed for at least three scheduled visits, where she underwent a usual 10-point NRS scoring for pain[47] and a 7-point Fatigue Severity Scale (FSS)[46,48] for fatigue evaluation. Initially, the patient reported an NRS score of 9.57 ±0.79 SD and an FSS of 6.57 ±0.78 SD. Then, she underwent one month of O_2-O_3-MAHT twice a week with 50 μg/ml in 200 ml of autologous blood by intravenous transfusion of the autologous ozonated blood and then twice a month as a maintenance therapy. Following a month of O_2-O_3-MAHT, the patient reported an NRS of 2.28 ±1.11 SD (- 76.12%, p = 0.00170, KW test) and an FSS of 1.57±0.79 SD (-76.09%, p = 0.00175 KW test). The patient did not report pain and fatigue for at least half past one year throughout the follow-up visits.

Case #3

Improvements were observed also for a 56-year-old female patient in post-menopausal stage, who was previously diagnosed with a Grade 2 estrogen-receptor positive invasive breast cancer and therefore subjected to surgery and radiotherapy. She was prescribed anastrozole (Arimidex®) 20 mg/ml a day therapy for four months, but after one single month, she suffered from spasms and musculoskeletal pain, with fatigue. An NRS score was 9.33±0.72 SD before entering a route of O_2-O_3-MAHT, upon counselling of her practitioner. Her initial FSS was 6.54 ±0.52 SD. Therefore, in

April 2019, the patient underwent O_2-O_3-MAHT (50 μg/ml in 200 ml) twice a week for one month.

One month later, the patient was asked to complete an NRS questionnaire. Her average values were 3.07 ±1.44 SD (-67.14%, $p < 0.00001$, KW test). Her FSS score was diminished to 2.91 ±0.83 SD (-55.55%, $p = 0.0008$). In a casual visit to our clinical healthcare center one year later, we asked about her health and wellbeing state, and she answered in a highly positive way, reporting no pain and no discomfort whatsoever.

Case #4

A 69-years old female entered our clinical service in the post-menopausal stage (in June 2019) and was previously diagnosed with a Grade 3 estrogen-receptor positive invasive breast cancer, for which she underwent a radical mastectomy with radiotherapy and a therapeutic regimen with anastrozole (Arimidex®) 20 mg/ml a day for three months. However, after 24 days of the anti-aromatase therapy, the patient suffered from general weakness and fatigue. Anastrozole was withdrawn from therapy, but fatigue and discomfort were persistent, compelling the patient to recur to NSAIDs. About three weeks after the Arimidex® removal, she was counseled to refer to our clinical healthcare service (Tirelli Clinical Group, Pordenone) for evaluating O_2-O_3-MAHT. At her entrance, an FSS questionnaire gave the average score (four sessions) of 6.53 ±0.64 SD. An O_2-O_3-MAHT uses 200 ml infusion of autologous blood with 50 μg/ml O_3, according to the previously published SIOOT protocol and following the same approach described for the other case reports here reported. The O_2-O_3-MAHT was performed twice a week for one month, and an FSS questionnaire was then performed (three replicates). The average score was 3.47±0.74 SD (- 46.94%, $p < 0.0001$ KW test). Even in this case report, the outcome of O_2-O_3-MAHT resulted in a significant reduction (about 50%) of the anti-aromatase-caused fatigue. The patients did not report any discomfort or musculoskeletal pain for the following six months in which she met our physicians.

Case #5

In older adults, the effect did not change at all. A 72-year-old female patient entered our clinical service in the post-menopausal stage (in August 2019) and was previously diagnosed with a Grade 3 estrogen-receptor-positive invasive breast with lung metastasis. She entered a therapeutic regimen with anastrozole (Arimidex®) 20 mg/ml once a day scheduled for three months. 32 days after the anti-aromatase therapy started, she reported general weakness, fatigue, and severe musculoskeletal pain, which compelled her to use NSAIDs. About two weeks later she was referred to our clinical services, where she underwent a cycle of O_2-O_3-AHT (50 μg/ml O_3 in 200 ml autologous blood), twice a week for five weeks. Upon entrance, she signed an informed consent, as indicated before with the other reported cases. Her NRS value (averaged) was 9.54 ±0.69 SD before starting the O_2-O_3-MAHT and decreased to 2.36 ±1.21 SD (-75.24%, $p = 0.00007$ KW test), whereas the FSS before O_2-O_3-MAHT was 6.72 ±0.65 SD and 40 days following O_2-O_3-MAHT starting, FSS lowered to 1.27 ±0.47 SD (- 81.08%, $p = 0.00091$). The patient did not report fatigue or pain anymore.

Case #6

Another 72-year-old female patient with a post-menopausal stage was previously diagnosed with a Grade 2 estrogen-receptor-positive invasive breast cancer (in March 2020). When treated with anastrozole (Arimidex®) 20 mg/ml once a day scheduled for five months, she suffered from severe pain in her musculoskeletal joints, following 65 days from the anti-aromatase therapy. Her NRS mean score was 8.63±0.81 SD. She underwent, after having joined our ethical recommendations and signed informed consent, a cycle of O_2-O_3-MAHT runs (45 μg/ml O_3 in 200 ml autologous blood), according to SIOOT protocols, twice a week for one month. At the end of O_2-O_3-MAHT her NRS lowered to 5.27 ±1.49 SD (- 38.95%, $p = 0.00011$, KW test). Table II shows a summary of the NRS and FFS values before and after O_2-O_3-MAHT.

Logistic Regression

Figure 1 shows the logistic regression (CI_{95}) for the evaluation of success in reducing pain following the O_2-O_3-MAHT or not ($x^2 = 13.4960$, $p = 0.0002$).

Logistic regression was performed considering a success (1) an output higher than 51%, both for fatigue and pain/discomfort.

Discussion

The therapy approach with O_2-O_3-MAHT reduced the musculoskeletal pain, in female subjects under anti-aromatase therapy by 66%

Table II. Changes in NRS and FFS scores following O_2-O_3-MAHT (*).

Case report pre-treatment	NRS before	NRS after	Delta %	FFS before	FFS after	Delta %
1[a]	9.71 ± 0.49	2.14 ± 0.90	−77.30% $p = 0.00177$	6.72 ± 0.65	1.91 ± 0.83	−71.62% $p = 0.0007$
2[b]	9.57 ± 0.79	2.28 ± 1.11	−76.12% $p = 0.00170$	6.57 ± 0.78	1.57 ± 0.79	−76.09% $p = 0.00175$
3[a]	9.33 ± 0.72	3.07 ± 1.44	− 67.14% $p < 0.00001$	6.54 ± 0.52	2.91 ± 0.83	−55.55% $p = 0.0008$
4[a]	N.E.	N.E.	N.E.	6.53 ± 0.64	3.47 ± 0.74	−46.94% $p < 0.0001$
5[b]	9.54 ± 0.69	2.36 ± 1.21	−75.24% $p = 0.00007$	6.72 ± 0.65	1.27 ± 0.47	−81.08% $p = 0.00091$
6[a]	8.63 ± 0.81	5.27 ± 1.49	−38.95% $p = 0.00011$	N.E.	N.E.	N.E.

(*) Mean ± SD; p evaluated with KW test; N.E. not evaluated, pre-treatment: [a]adjuvant; [b]metastatic.

(66.95%) within the first month of oxygen-ozone therapy, accounting for only 8 sessions of ozone autohemotherapy. A comparable value was obtained for fatigue (66.26% ±14.43 SD, median = 71.62%). Table II summarizes data (Figure 1). In a cohort of 13 cases, the six presented cases were the most significant according to the eligible criteria; moreover, 5 of them left the study before completing the autohemotherapy runs, one left the clinical service, and two did not respond to the ozone therapy. Logistic regression assessed the success of O_2-O_3-MAHT in significantly re-

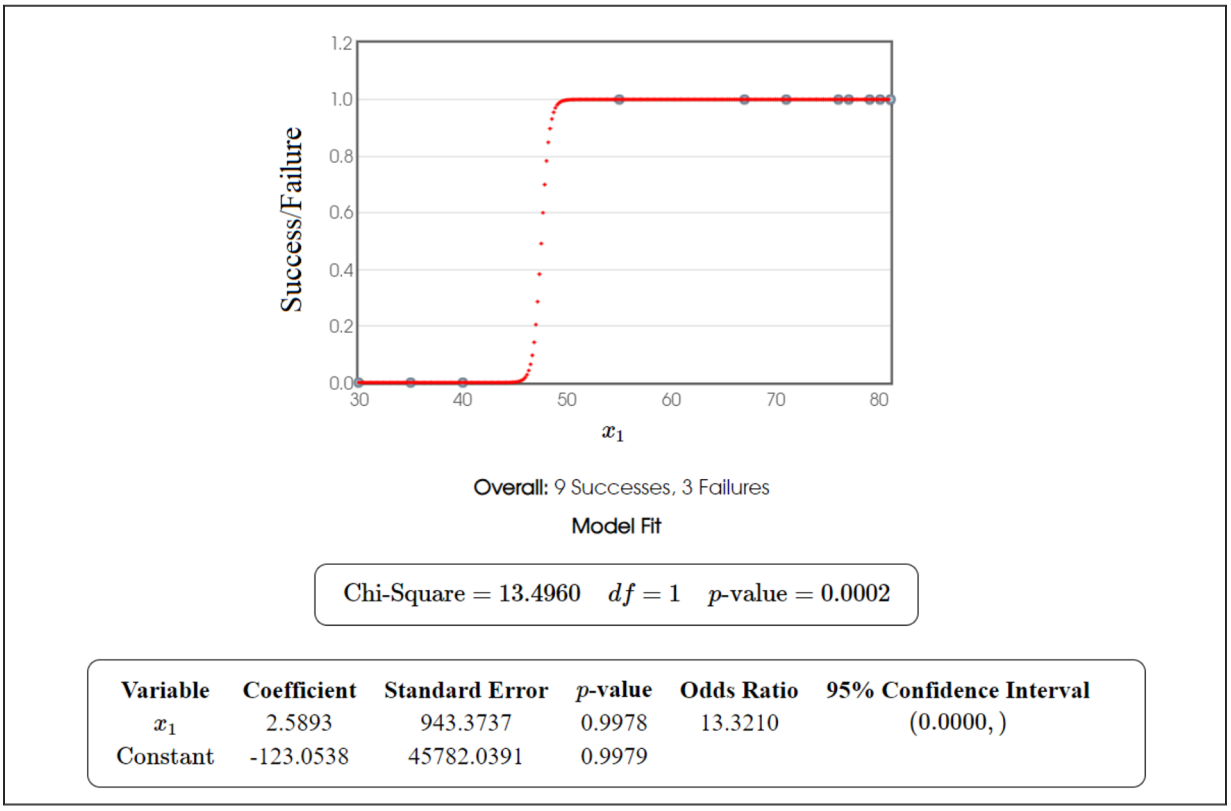

Figure 1. Failures/Success logistic regression plot for a non-linear statistical analysis of 12 categorical responses (dependent variable), on two values: '0' and '1' representing an outcome such as success/failure, for each patient if treated or non-treated with the O_2-O_3-MAHT in a forecast analysis (SPSS v. 24 IBM Corp., Armonk, NY, USA).

ducing pain and fatigue in these patients, at least completely, in 75% of them. The 10-item pain NRS scoring median value in these patients was 9.23 before the O_2-O_3-MAHT and dropped down to 2.36 following one month of ozone therapy. Fatigue dropped from 6.62 ±0.09 SD to 2.22 ±0.93 SD, following at least one month of O_2-O_3-MAHT.

The ability of ozone to reduce pain and fatigue in those subjects upon anastrozole therapy is yet far to be fully elucidated. A possibility may be searched in the anti-inflammatory and immune modulatory activity of ozone and its lipid mediators[49,50]. Estrogens counteract the ozone-induced oxidative stress[51], and particularly in post-menopausal women, estrogens should act as anti-inflammatory hormones[52,53]. When an anti-aromatase pharmaceutical drug is used, the estrogen-mediated anti-inflammatory property is particularly compromised but, in these circumstances, estrogen deficiency might induce mitochondrial damage[54], which therefore may re-activate mitochondria biogenesis[55].

Excessive production of ROS, as occurring following arsenic trioxide or doxorubicin (Adriamicin®), may be invoked to kill cancer cells. Actually, some PUFA-derived LOPs, usually induced by ozonated blood, might sensitize cancer cells (such as in breast cancer) to ROS-inducing anticancer agents, such as 4-HNE[56]. It is therefore plausible that ozone, *via* its lipo-peroxide intermediates, induces mitochondria biogenesis and the activation of a TGF-β/IL-10 anti-inflammatory cytokines, which are reported as a decrease in the NRF scales, as described in this manuscript[56].

Limitations

A major limitation of this study is the paucity of cases described. Considering that this should be a pilot study to be further implemented with a higher number of patients, we attempted this therapy accounting on the ability of ozone, in its previous mixture oxygen-ozone, to sedate pain, discomfort and reduce fatigue and muscle weakness, causing rapid relief of these symptoms and allowing people to come back to their health and wellbeing daily lives.

Conclusions

The O_2-O_3-MAHT reduced the musculoskeletal pain and fatigue in female affected by breast cancer and upon ongoing treatment with anti-aromatase anastrozole (Arimidex®). This reduction was higher than 66% in terms of 10 points-NRS scale and of 7-point FSS scale and persistent for many months, even without therapy persistence.

Conflict of Interest

The authors declare that they have no conflict of interests.

Acknowledgements

We thank Dr William Ghersley for his precious aid in the English language.

Ethics Approval

The study was conducted according to the Declaration of Helsinki and approved by the Ethical Committee of the Tirelli Clinical Group (ISS Prot. 56/2020).

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Availability of Data and Materials

Any data set is available on request to the Corresponding Author.

Funding

None.

Authors' Contribution

UT, MB and SC conceived, performed and elaborated raw data and results, UT, MB and MF supervised and validated the research study, LV, MF contributed to the oxygen-ozone therapy performance, SP, elaborated and revised the manuscript, SC wrote the manuscript, revised and validated the manuscript, elaborated the statistics.

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