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Long-Term Effects of Ozone Treatment in Patients with Persistent Numbness and Tingling Secondary to Chemotherapy-Induced Peripheral Neuropathy. A Retrospective Study

Bernardino Clavo, MD, PhD[1,2,3,4,5,6], Delvys Rodríguez-Abreu, MD, PhD[7], Saray Galván-Ruiz, MD[1], Mario Federico, MD, PhD[1], Angeles Cánovas-Molina, RN[1,2], Yolanda Ramallo-Fariña, MSc[2,8,9], Carla Antonilli, MD[1], Gretel Benítez, MD[7], Himar Fabelo, BEng MSc, PhD[2,3], Carla García-Lourve, RN, MRes[1,2], Damián González-Beltrán, CNS, MSc[1,2], Ignacio J. Jorge, MD, PhD[1], Francisco Rodríguez-Esparragón, BSc, PhD[1,2,4,5], and Gustavo M. Callico, MEng, PhD[3]

Abstract

Background: Numbness and tingling secondary to chemotherapy-induced peripheral neuropathy (CIPN) are frequent side effects that limit chemotherapy treatment and quality of life. Successful treatments for CIPN are limited. This preliminary report shows the potential long-term effects of ozone treatment in the management of persistent numbness and tingling secondary to CIPN. **Methods:** Ozone treatment was administered by rectal insufflation in 15 patients (female/male: 8/7, age: 66 years old) suffering from persistent numbness and tingling secondary to grade-2 or grade-3 CIPN. Planned ozone treatment consisted of 40 sessions over 4 months. The initial concentration of 10 μg/mL was progressively increased to 30 μg/mL. The initial gas volume of 180 mL/session was progressively increased to 300 mL/session if tolerated. Before and after ozone treatment, and at 3- and 6- months after the end of treatment, they were assessed (i) the grade of CIPN-toxicity, and (ii) the self-reported decrease in numbness and tingling. **Results:** After ozone treatment, 47% of patients experienced a decrease in the grade of CIPN-toxicity ($P = .016$), and 67% of patients reported a decrease in numbness and tingling ≥50% ($P = .002$). These effects were maintained at 3- and 6- months after the end of O_3T. **Conclusions:** In this retrospective report, patients with persistent numbness and tingling secondary to CIPN showed clinically relevant and long-term improvements after ozone treatment. The magnitude and duration of the observed effects merit further research and support our ongoing clinical trials.

Keywords
numbness and tingling, paresthesias, chemotherapy-induced peripheral neuropathy, grade of toxicity, side effects, cancer survivors, ozone treatment, oxidative stress modulation, Nrf2

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Background

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect of several chemotherapy drugs. The main symptoms of CIPN include pain, numbness, tingling, changes in sensation, an increase or decrease in sensitivity to touch, alterations in temperature, pressure, or proprioception, or the loss of coordination. Between 19% and 85% of cancer patients will present with CIPN after different neurotoxic chemotherapies, as well as 70% to 100% of patients after treatment with platinum-based drugs.[1] Early presentation of CIPN can lead to the delay, reduction, or even interruption of the initially planned chemotherapy. After the end of chemotherapy, chronic CIPN leads to significant alterations in health-related quality of life. Additionally, functional limitations in hands and feet secondary to CIPN may

be associated with an increased risk of injuries such as burns, falling, dropping objects, trauma, and disability,[2,3] as well as the increased utilization of healthcare resources (outpatient visits, hospital stays)[4] and a higher economic burden.[5] Unfortunately, there are no clinically relevant approaches for preventing CIPN or treating established CIPN, with the exception of duloxetine, which has a limited effect in the treatment of CIPN-related pain.[6-9] The development and evaluation of novel strategies to mitigate and manage the chronic side effects of cancer therapy (including CIPN) have been established as urgent research areas by the American Society of Clinical Oncology (ASCO).[10]

Chemotherapy can damage nervous system structures and cause CIPN by several mechanisms; among these are chronic oxidative stress and neuroinflammation.[1,8,11-13] It has been described how ozone treatment (O_3T) could be used to enhance the effect of chemotherapy and radiotherapy[14-19] as well as in the prevention and management of side effects of radiotherapy,[20-23] chemotherapy,[24] and surgery.[14,25] Modulation of oxidative stress and inflammation are some of the most relevant mechanisms of action of O_3T, and they have also been described in the prevention and improvement of CIPN.[24,26]

The aim of this report is to show the long-term effects of O_3T as an adjuvant treatment in the palliative/symptomatic management of patients with chronic numbness and tingling secondary to CIPN.

Methods

Patients and Design

This before/after retrospective study shows the results of all patients treated with rectal O_3T because of chronic and refractory numbness and tingling secondary to CIPN and followed up in our multidisciplinary Chronic Pain Unit between June 2019 and May 2023. The cohort comprised 15 patients, 7 males and 8 females, with a median age of 66 (between 36 and 76) years old. The grade of CIPN-toxicity was grade 2 ($n=8$) or grade 3 ($n=7$) according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 classification of the National Cancer Institute of the USA.[27] The Health Care Ethics Committee at our hospital previously evaluated the compassionate use of O_3T for patients with refractory symptoms. This study was approved by the Provincial Research Ethics Committee of Las Palmas, Spain (Ref 2019-288-1). Informed written consent was obtained from all patients.

All patients were submitted by their oncologist with the clinical diagnosis of CIPN after the commencement of chemotherapy. CIPN was not secondary to neurological involvement or compression by metastatic or primary tumors. More than half of the patients suffered from pelvic tumors, and all these patients had control of primary tumors when submitted for ozone treatment. This study did not include patients with colostomy. Further details about general and patients' clinical characteristics are presented in Tables 1 and 2, respectively.

Ozone Treatment

O_3T was administered by rectal insufflation on an outpatient basis if there was no evidence of tumor progression. Ozone (an O_3/O_2 mixture) was obtained from clinical-grade oxygen using 2 medical ozone generators: (i) Ozonosan Alpha-plus® from Hänsler Medical GmbH (Iffezheim, Germany), and (ii) Ozonobaric P® from Sedecal (Madrid, Spain). The O_3/O_2 gas mixture obtained was administered by rectal insufflation. The procedure has been previously described.[28] In brief, we used a rectal cannula and standard 60 mL syringes. Concentrations of O_3/O_2 gas were progressively increased from 10 to 30 µg/mL (µg of O_3 per mL of O_2); the gas volume for insufflation depended on the patient's tolerance of bowel bloating, and it was progressively increased from a 180 mL/session to a 300 mL/session if tolerated (as was the case for most patients). Therefore,

[1]Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain
[2]Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC), Las Palmas de Gran Canaria/Tenerife, Spain
[3]University of Las Palmas de Gran Canaria (ULPGC), Las Palmas de Gran Canaria, Spain
[4]Instituto Universitario de Enfermedades Tropicales y Salud Pública de Canarias de la Universidad de La Laguna, La Laguna, Tenerife, Spain
[5]CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain
[6]Spanish Group of Clinical Research in Radiation Oncology (GICOR), Madrid, Spain
[7]Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Las Palmas de Gran Canaria, Spain
[8]Network for Research on Chronicity, Primary Care, and Health Promotion (RICAPPS), Barcelona, Spain
[9]Servicio de Evaluación y Planificación del Servicio Canario de Salud (SESCS), Santa Cruz de Tenerife, Spain

Corresponding Authors:
Bernardino Clavo, Research Unit, Hospital Universitario de Gran Canaria Dr. Negrín, Barranco la ballena s/n, Las Palmas de Gran Canaria 35019, Spain.
Email: bernardinoclavo@gmail.com

Francisco Rodríguez-Esparragón, Research Unit, Hospital Universitario de Gran Canaria Dr Negrin, Barranco la ballena s/n, Las Palmas de Gran Canaria 35019, Spain.
Email: afrodesp@gmail.com

Table 1. General Clinical Characteristics of the Study Group.

Gender	Female	8
	Male	7
Age (years old)	Female	Median 58 (range: 39-76)
	Male	Median 68 (range: 36-75)
Tumor location	Colon and rectum	5
	Gynecological tumors	4
	Lung	2
	Lymphoma	2
	Breast	1
	Head and neck	1
Chemotherapy drugs (number of patients)	Platinum-based drugs (oxaliplatin, carboplatin, cisplatin)	11
	Paclitaxel	5
	Anthracycline drugs (doxorubicin, epirubicin)	4
	Vinca alkaloids (vincristine, vinblastine)	2
	Pembrolizumab	2
	Brentuximab Other used drugs (ifosfamide, etopoxide, bleomycin, dacarbzine, cyclophosphamide, 5-fluorouracil, irinotecan, pemetrexed)	1
Chemotherapy (CT) comments (number of patients)	CT withdrawal because of CIPN	4
	CT dose reduction because of CIPN	3
	2nd or 3rd line CT during ozone treatment	2*

Abbreviation: CIPN, Chemotherapy induced peripheral neuropathy.
*Two patients. with initial diagnosis of colon and rectum carcinoma were under 2nd or 3rd line chemotherapy (CT) during ozone treatment due to systemic disease, without primary pelvic tumor.

after the 9th session, the total amount of ozone administered in each session was planned at 9000 µg (for 300 mL volume). The initially planned treatment consisted of 40 sessions over 4 months, with 3 sessions per week during the first 2 months and 2 sessions per week after this, although the final number of O_3T sessions could vary according to the clinical evolution.

Assessment of Grade of Toxicity and Numbness and Tingling

Grade of CIPN-toxicity was assessed according to the CTCAE v.5.0 scale of the National Cancer Institute of the U.S.A.[27] Grade-0: no toxicity; Grade-1: toxicity without symptoms or mild symptoms; Grade-2: moderate symptoms, limiting instrumental activity of daily living; Grade-3: severe symptoms, limiting self-care activity of daily living, requiring hospitalization or elective medical intervention; Grade-4: life-threatening consequences, with urgent intervention indicated; and Grade-5: death. The grade of toxicity was assessed at 4 time-points: (i) before O_3T, (ii) at the end of the O_3T, (iii) 3 months after the end of the O_3T, and (iv) 6 months after the end of the O_3T. Additionally, it was also recorded if the grade of toxicity improved or did not improve.

The percentage of improvement in any kind of symptoms (numbness and tingling included) is a usual clinical record in our Chronic Pain Unit, and it is self-evaluated by patients. For these assessments, the basal intensity of numbness and tingling before the commencement of O_3T was established for each patient as the maximum value (100%) for further assessments (basal value). Regarding their basal intensity of symptoms (100%) and the minimum value (0%) as the complete absence of numbness and tingling symptoms, patients self-reported the percentage of residual numbness and tingling (100 points scale, range from 0 to 100) in a similar way to the visual analog scale (10 points scale, range from 0 to 10). Additionally, it was also recorded if the improvement in numbness and tingling was $\geq$50% or not.

Table 2. Patients' Clinical Characteristics.

Patients	Diagnosis, chemotherapy, and comments
1	Uterine adenosarcoma. TX: S + RT + CT (Ifosfamide + Doxorubicin).
2	Endometrial serous-papillary carcinoma. TX: S + RT + CT (Cisplatin + Paclitaxel)
3	Breast lobulillar carcinoma. TX: S + RT + CT (5-Fluorouracil + Epirubicin + Cyclophosphamide + Paclitaxel)
4	Ovarian serous carcinoma + endometrial carcinoma. TX: S + RT + CT (Carboplatin + Paclitaxel, 50% reduction was required).
5[a]	Squamous cell carcinoma at the base of the tongue. TX: S + CT (Cisplatin + 5-Fluorouracil + Cetuximab, suspension of the last CT-cycle was required. O_3T during TX with Pembrolizumab because of previous Stage IV melanoma.
6[b]	Colon adenocarcinoma. TX: S + CT. 1st line CT: Capecitabine + Oxaliplatin + Bevacizumab (Oxaliplatin withdrawal was required). O_3T during the second-line of CT[b]: Folinic acid + 5-Fluorouracil + Irinotecan + Aflibercept.
7	Colon adenocarcinoma. TX: S + CT (Folinic acid + 5- Fluorouracil + Oxaliplatin, 75% reduction was required).
8[b]	Colon adenocarcinoma Stage IV. TX: S + CT. 1st line CT: Folinic acid + 5- Fluorouracil + Oxaliplatin. 2nd line CT: Folinic acid + 5- Fluorouracil + Irinotecan (reductions were required because of hematologic toxicity and neuropathy). O_3T during the third-line of CT[b]: Folinic acid + 5- Fluorouracil + Oxaliplatin (40% reduction) + Cetuximab
9	Non-Hodgkin's lymphoma of parotid. TX: S + RT + CT (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone).
10	Colon adenocarcinoma. TX: S + CT: (Folinic acid + 5-Fluorouracil + Oxaliplatin).
11	Lung adenocarcinoma. TX: S + RT + CT (Carboplatin + Etoposide).
12	Rectum adenocarcinoma. TX: RT + CT (Capecitabine) + S + CT (Folinic acid + 5-Fluorouracil + Oxaliplatin).
13	Hodgkin's disease Stage IV-B. TX: CT. 1st line CT (Doxorubicin + Bleomycin + Vinblastine + Dacarbazine); 2nd line CT (Brentuximab + autologous transplant of hematopoietic progenitors + Brentuximab maintenance, which was stopped because of CIPN progression).
14	Lung adenocarcinoma. TX: RT + CT. 1st line CT: Carboplatin + Paclitaxel. 2nd line CT: (Carboplatin + Pemetrexed + Pembrolizumab + maintenance with Pembrolizumab + Pemetrexed, which was stopped because of CIPN progression).
15	Uterine carcinosarcoma. TX: S + RT + CT (Carboplatin + Paclitaxel).

Abbreviations: TX, Treatment; S, surgery; RT, radiotherapy; CT, chemotherapy; O_3T, ozone therapy.
[a]Patient #5 rejected radiotherapy for treatment of the carcinoma at the base of the tongue.
[b]Patients #6 and #8 received O_3T during further neurotoxic treatment of chemotherapy because of systemic tumor progression: patient #6 during second-line chemotherapy after the failure of the first-line of chemotherapy (after the failure of the first option of treatment), and patient #8 during the third-line chemotherapy after failure of the first and second lines of chemotherapy.

Variables were assessed during the routine medical visits at the Chronic Pain Unit, under usual and homogeneous conditions. Variables were assessed at each of the following 4 time-points: (i) before O_3T, (ii) at the end of the O_3T, (iii) 3 months after the end of the O_3T, and (iv) 6 months after the end of the O_3T.

Statistical Analysis

The IBM® SPSS® software package (version 15 for Microsoft Windows) was used for statistical analyses. The main variables did not follow a normal distribution, and non-parametric tests were used in this study despite their lower statistical power. All data are described as the median (quartile 2) and quartiles 1 and 3 (Q1-Q3). Correlations between the grade of toxicity and the scores of numbness and tingling were assessed using Spearman's rho. For numeric variables (grade of CIPN-toxicity and percentage of residual numbness and tingling), the overall comparison among the repeated 4 time-points of assessment was analyzed using the Friedman test. For qualitative variables (patients "with or without" improvement in the grade of toxicity and patients "with or without improvement ≥50%" in numbness and tingling) the overall comparison among the 4 time-points of assessment was analyzed using the Cochran's Q test. Regarding the basal status before O_3T, paired comparisons were conducted with the exact (significance) Wilcoxon rank test for numeric variables and with the exact (significance) McNemar's test for qualitative variables. Though more conservative than asymptotic tests, exact tests were used due to the small sample size. *P*-values of $<.05$ were considered statistically significant.

Results

The median time from the initiation of symptoms to the commencement of O_3T was 21 months (Q1-Q3: 11-48). One patient started experiencing CIPN symptoms 10 months after the end of chemotherapy, and the remaining patients began experiencing symptoms before the end of chemotherapy.

The median duration of O_3T was 17 weeks (Q1-Q3: 16-20), and the median number of O_3T sessions was 40 (Q1-Q3: 37-40). One patient with improvement 3 months after O_3T did not complete the 6-month follow-up because of metastatic tumor progression.

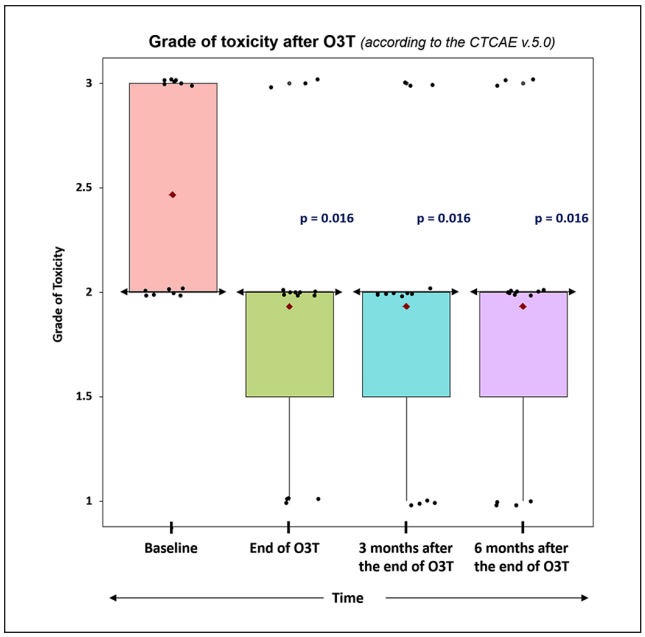

Figure 1. Grade of numbness and tingling toxicity.
Grade of toxicity after ozone therapy (O_3T) related to numbness and tingling (according to the Common Terminology Criteria for Adverse Events (CTCAE v.5.0) classification). Overall, the comparison of the grade of toxicity among the 4 time-points of assessment was statistically significant (Friedman test: $P < .001$). The median value was: 2 (Q1-Q3 = 2-3) before O_3T, 2 (Q1-Q3 = 1-2) at the end of O_3T (exact significance Wilcoxon rank test: $P = .016$), and it was maintained at 3- and 6- months after the end of O_3T. Box: quartiles 1 to 3. Black points: in-dividual values. Median: double horizontal arrow; Mean: red diamond.

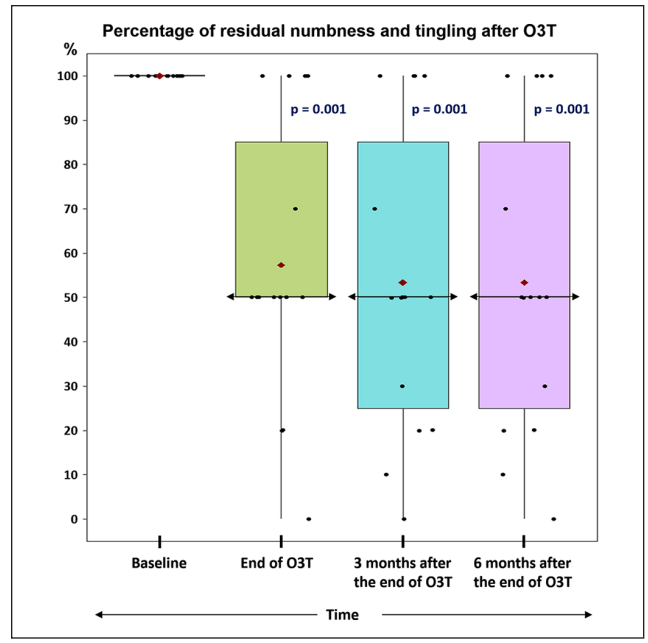

Figure 2. Percentage of residual numbness and tingling after ozone therapy (O_3T).
For each patient, the baseline value of numbness and tingling was established as 100%. During the follow-up, it was assessed the percentage of residual numbness and tingling according to the individual basal level. Overall, the comparison of the residual numbness and tingling among the 4 time-points of assessment was statistically significant (Friedman test: $P < .001$). The median value was: 50% (Q1-Q3 = 50%-100%) at the end of O_3T (exact significance Wilcoxon rank test: $P = .001$), and it was maintained at 3- and 6- months after the end of O_3T. Box: quartiles 1 to 3. Black points: individual values. Median: double horizontal arrow; Mean: red diamond.

Overall, the comparison of patients "with or without" improvement in the grade of toxicity among the 4 time-points of assessment was statistically significant ($P < .001$). The number of patients who experienced a decrease in the grade of toxicity was 7 out of 15 (46.7%) at the end of O_3T ($P = .016$), and it was maintained at 3- and 6- months after the end of O_3T. Overall, the comparison of the grade of toxicity among the 4 time-points of assessment was statistically significant ($P < .001$). The median value was 2 (Q1-Q3: 2-3) before O_3T, 2 (Q1-Q3: 1-2) at the end of O_3T ($P = .016$), and it was maintained at 3- and 6- months after the end of O_3T. (Figure 1).

Overall, the comparison of patients "with or without improvement ≥50%" in numbness and tingling among the 4 time-points of assessment was statistically significant ($P < .001$). The number of patients who reported a "decrease in numbness and tingling ≥50%" was 10 out of 15 (66.7%) at the end of O_3T ($P = .002$), and it was maintained at 3- and 6- months after the end of O_3T. Four patients did not obtain any improvement in numbness and tingling. One patient reported a 30% improvement of the basal condition and was considered as no-improvement (improvement <50%). Overall, the comparison of the residual numbness and tingling among the 4 time-points of assessment was statistically significant ($P < .001$). The median value of residual numbness and tingling was 50% (Q1-Q3: 50%-100%) at the end of O_3T ($P = .001$), and it was maintained at 3- and 6- months after the end of O_3T (Figure 2).

After O_3T, there was a correlation between the grade of toxicity (grade 2 vs grade 3) and the scores of numbness and tingling. This way, patients with grade 2 toxicity showed a lower percentage of residual numbness and tingling at the end of the O_3T (rho = .651, $P = .009$), 3 months after the end of O_3T (rho = .723, $P = .002$), and 6 months after the end of O_3T (rho = .658, $P = .011$).

For each of the patients, the grade of toxicity and intensity of numbness and tingling symptoms shown at the end of the O_3T therapy did not change over time and remained the same at 3- and 6- months follow-up, without impairment or further improvement.

Age, gender, and the duration of CIPN symptoms before the beginning of the O_3T were not significantly associated with the effect of O_3T.

As additional individual observations, this study showed: (i) 2 patients reported relevant improvement in tolerance to touch and holding hot/cold things, (ii) 1 patient without

Table 3. Months with Symptoms and Patient-Reported Changes in Numbness, Tingling, and Grade of Toxicity at the End of the Ozone Treatment (O_3T).

Patients	Months with symptoms before O_3T	O_3 sessions	Numbness and tingling. Basal % before O_3T	Numbness and tingling. Residual % after O_3T**	*Grade of toxicity before O_3T	*Grade of toxicity after O_3T**
1	8	50	100	49[a]	3	2
2[b]	4	40	100	49[a]	3	2
3	60	23	100	100	3	3
4	13	40	100	100	2	2
5[c]	12	40	100	100	2	2
6[b,d]	11	12	100	49[a]	2	2
7[b]	48	40	100	100	2	2
8[d,e]	21	61	100	20	2	1
9[f]	174	40	100	0	2	1
10[e]	27	40	100	20	2	1
11	14	40	100	49[a]	2	2
12	70	37	100	49[a]	3	3
13	23	30	100	70	3	3
14	23	40	100	49[a]	3	1
15	7	40	100	49[a]	3	2

Abbreviation: O_3T, ozone treatment.
[a]Patients that reported residual numbness and tingling lower than half of the initial condition (<50%), but who were unable to establish a more accurate percentage. The value of 49% of residual symptoms was established because of it was considered the most unfavorable value for our study.
[b]Patients #2, #6, and #7 reported improvements in their sense of balance after O_3T.
[c]Patient #5 reported improvements in desire and sexual potency after O_3T.
[d]Patients #6 and #8 received O_3T during further neurotoxic treatment of chemotherapy because of systemic tumor progression.
[e]Patients #8 and 10 reported improvements in their tolerance to cold and touching/picking up frozen things
[f]Patient #9 reported no numbness or tingling at the end of O_3T (improvement of 100%); however, we established grade 1 toxicity because the other CIPN symptom (pain) did not disappear completely.
*Chemotherapy-induced peripheral neuropathy (CIPN) grade of toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 of the US National Cancer Institute: grade 1: mild symptoms; grade 2: moderate symptoms, limiting instrumental activities of daily life (ADL); grade 3: severe symptoms, limiting self-care in ADL; grade 4: life-threatening consequences; urgent intervention.
**Numbness and tingling and grade of toxicity at the end of O_3T did not change at 3- and 6- months after the end of O_3T.

improvement in numbness and tingling reported recovery of the sexual desire and potency, and (iii) 3 patients reported relevant improvements in balance disorders, which were probably secondary to improvements in feet proprioception despite experiencing no improvement in numbness and tingling. Therefore, 2 out of 4 patients without improvement in numbness and tingling reported improvements in other CIPN-related symptoms. The additional improvements in these other symptoms were also maintained at the 6-month follow-up appointment after the end of the O_3T.

Details about months with symptoms and individual results at the end of O_3T are presented in Table 3.

Discussion

In our study, rectal O_3T improved self-reported numbness and tingling in patients with chronic CIPN and decreased the grade of toxicity associated with these symptoms, with a long-lasting effect.

CIPN is a frequent side effect of chemotherapy; it often becomes chronic, difficult to manage, and limits patients' quality of life. There are no established treatments for numbness and tingling.[6-9] The treatment with the best evidence is duloxetine in "painful" CIPN, although with small effect and potential adverse effects.[6,7] The potential benefits of non-pharmacological approaches (exercise, acupuncture, or scrambler therapy) require confirmatory studies[6]. So, further research in this field is required.[10]

In our study, the administration of O_3T in patients suffering from long-term CIPN was associated with: (i) a clinically relevant decrease in numbness and tingling in two-thirds of patients, and (ii) a decrease in the grade of toxicity according to the CTCAE scale, which was improved in nearly half of patients (it should be noted that improvements in symptoms reported by patients is not always sufficient to change the grade of toxicity according to the CTCAE scale).

We would like to highlight 2 aspects of our study. First, regarding the magnitude of the observed effect, two-thirds of patients reported a decrease in numbness and tingling equal to or higher than 50% after receiving the O_3T, which we considered clinically relevant. Second, we note the length of the O_3T effect, which was maintained at 6 months (24 weeks) after the end of O_3T (41 weeks after the

beginning of O_3T). This protracted effect compares well with the effect described for duloxetine in painful CIPN (half of its small effect was lost 1 week after the treatment ended),[7] the improvement reported 8 weeks after the end of scrambler therapy,[29] or the improvement reported 12 weeks after the end of acupuncture treatment.[30] The magnitude and duration of the effect of O_3T in terms of numbness and tingling concur with the effects already described: (i) 6 months after the end of O_3T in painful CIPN,[28] (ii) 9 months afterward in pelvic pain secondary to radiotherapy,[31] and (iii) after several years in patients with refractory hemorrhagic radiation-induced proctitis.[32]

On the other hand, CIPN can lead to significant alterations in sensitivity to touch, temperature, pressure, proprioception, or coordination, significantly limiting patients' quality of life. These symptoms have been associated with (i) balance deficits, worsening function, increasing disability, and higher fall risk,[2,3] and (ii) more days spent in the hospital and emergency department, more outpatient visits, and double healthcare costs of non-CIPN controls.[4,5] The long-term improvement in numbness and tingling observed in our current study would suggest a potential long-term reduction in the risk of associated injuries. This agrees with another study in patients treated because of side effects of cancer treatments, which described how O_3T improved all domains of the EQ-5D-5L questionnaire of health-related quality of life (HRQoL), including "mobility," "self-care capacity," and "ability to carry out the activities of daily living."[33] The results in these dimensions directly translate to the improvement of HRQoL, but they also suggest a theoretical decrease in the risk of further injuries.

Multiple factors are involved in the pathogenesis of CIPN, such as altered ion channel activity (Na, K, Ca, transient receptor potential -TRP- channels), myelin sheath damage and axonal degeneration, mitochondrial damage, microtubule disruption, DNA damage, or apoptosis. Related to those factors, 2 other relevant mechanisms are the local increase of oxidative stress and induction of immunological alterations (activation of toll-like receptors -TLR-), which lead to increased production of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, TNFα, IFN-γ) and neuroinflammation.[1,8,11-13] Additionally, some studies have suggested the potential role of gut microbiota in CIPN.[34,35]

Recently, the potential role of O_3T in the modulation of oxidative stress and inflammation in the management of CIPN has been described in detail.[26,36] Briefly, during treatment with O_3T by rectal insufflation, ozone interacts with polyunsaturated fatty acids (PUFAs), antioxidants, and other components of glycocalyx and mucoproteins to generate reactive species of oxygen (ROS) and lipid oxidation products (LOPs), which interact with the PUFAs of cell membranes of the intestinal mucosa. The subsequent production of additional LOPs and aldehydes (as 4-hydroxynonenal (4-HNE)) can reach distant tissues. Finally, at the local or systemic levels, O_3T can lead to a transient upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2), which induces an enhancement of adaptive antioxidant mechanisms. Nrf2 can down-regulate NF-kB expression, leading to a potential decrease in pro-inflammatory cytokine production. In addition, it has been described that ozone can alleviate neuropathic pain by upregulation of the adenosine 5'-monophosphate-activated protein kinase (AMPK) / suppressors of cytokine signaling (SOCS) 3, which can inhibit the TLR4-mediated inflammatory pathway.[37] In this way, the modulation of oxidative stress and inflammation by O_3T is a non-specific "indirect effect," which follows a hormetic dose-response relationship similar to that described for Nrf2[38]: (i) very low ozone concentrations can have no effect (very low production of ROS, LOPs, and 4-HNE would be eliminated by the preexistent free-radical scavengers and it would not induce a further increase of antioxidants), (ii) very high concentrations can lead to excessively high production of free radicals and adverse side effects, and (iii) only low/moderate ozone concentrations can produce ROS, LOPs, and 4-HNE mediators enough to induce an adaptive induction of antioxidant mechanisms, with a final beneficial effect.[39-43] These action mechanisms support the results obtained in previous works using O_3T to modulate oxidative stress and inflammation-mediated damage, as in the chronic side effects of radiotherapy[31,32] or CIPN[28,33] we described above. Finally, according to the above-mentioned studies,[34,35] if O_3T by rectal insufflation can modify gut microbiota (as an additional mechanism of action in CIPN) it will merit further focused research.

Meteorism and bowel bloating were the main side effects of rectal gas insufflation, which usually disappear spontaneously or after gas release by patients.[28,44]

It is not known the optimal dose of ozone to be administered for CIPN. Most of the experimental and clinical studies with ozone rectal administration use 10 to 30 microg/mL, and very low concentrations do not induce any adaptive stimulus or clinical benefit.[28,32,33,41] However, in the future, it could be possible that a personalized optimal dose could be selected for each patient, based on its basal antioxidant capacity, oxidative stress, or proinflammatory status (O_3T with personalized medicine approach). Further research in this field is required.

Autohemotherapy is another route of O_3T for obtaining a similar systemic effect, which avoids the meteorism, bowel bloating, or subjective inconveniences of rectal insufflation. For those reasons, autohemotherapy could be better accepted for some patients. As with rectal O_3T, there are also few studies using O_3T by autohemotherapy in the management of cancer patients. They could be highlighted: (i) some old reports showing improvement of patients' HRQoL using O_3T during chemotherapy for lung cancer[45] and head and neck cancer[46]; (ii) one report of O_3T as support and palliative treatment in patients with fatigue because of different cancers,[47] and (iii) a more recent report also showing improvement on breast cancer patients with fatigue and musculoskeletal pain secondary to aromatase inhibitors

treatment.[48] However, except for patients with colostomy, we prefer to use rectal administration in cancer patients because of its lower risks, as we have described previously.[28] Briefly, cancer survivors with chronic symptoms are frail patients, usually with difficult venous access for repetitive punctions, blood extraction, and reinfusion several times per week, for several months (as it is required for autohemotherapy). Additionally, some usual events in these patients could be erroneously attributed to O_3T by a venous approach, but harder to attribute to rectal insufflation.[28]

The main limitations of our study are as follows.

(i) It was a non-randomized clinical trial with a small sample size. This retrospective study evaluated patients treated with symptomatic and compassionate intentions. Further randomized clinical trials are ongoing to confirm the potential effects of O_3T in patients with CIPN, 1 focused on "painful" CIPN (NCT04299893, EU CT ID: 2024-518021-16-00) and another 1 focused on "numbness and tingling" (NCT06706544, EU CT ID: 2024-517196-20-00).

(ii) A potential placebo effect could not be completely ruled out. However, in these patients with refractory symptoms after 2 years of conventional treatment, the magnitude and duration of the observed decrease in numbness and tingling after O_3T make a placebo effect unlikely. The association after the end of the O_3T between the CTCAE grade of toxicity (graded by the physicians) and the percentage of numbness and tingling self-reported by patients at the different time-points, could offer additional support against a potential placebo effect.

(iii) This study evaluated the "percentage of improvement" in numbness and tingling self-reported by patients, which is a not validated or standardized instrument of measure. The "percentage of improvement" regarding the baseline situation is an easy-to-understand measure for patients usually recorded in our Chronic Pain Unit to assess different symptoms. The above-mentioned association between the "percentage of improvement" in numbness and tingling and the CTCAE "grade of toxicity" supports the potential relevance of this outcome measure. Our ongoing clinical trials will evaluate validated questionnaires. Additionally, to better evaluate the alterations and evolution of CIPN more objectively and in a non-invasive fashion, we are currently studying the potential role of different imaging technologies, such as digital infrared thermal imaging and hyperspectral imaging; we have developed a customized system for this purpose, starting with the remote measurement of oxygen saturation.

(iv) This research did not evaluate the potential dimensions of gender in numbness and tingling secondary to CIPN.

Conclusions

This preliminary study suggests that adjuvant ozone treatment could offer long time alleviation of numbness and tingling in patients with chronic CIPN, symptoms. The potential role of adjuvant ozone treatment in the management of these symptoms merits further research and supports our ongoing randomized clinical trials.

Authors' Note

Himar Fabelo is also affiliated to Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain.

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Author Contributions

Conceptualization: B.C., D.R.-A., F.R.-E., and G.M.-C.; formal analysis: B.C., and Y.R.-F.; methodology: B.C., Y.R.-F., F.R.-E., and G.M.-C.; initial management and oncology follow-up: D.R.-A., S.G.-R., M.F., C.A., and G.B.; treatment with ozone therapy: B.C., A.C.-M., C.G.-L., D.G.-B., and I.J.J.; writing—original draft: B.C., D.R.-A., M.F., Y.R.-F., H.F., and F.R.-E.; writing—review, editing, and approval of the final version: B.C., D.R.-A., S.G.-R., M.F., A.C.-M., Y.R.-F., C.A., G.B., H.F., C.G.-L., D.G.-B., I.J.J., F.R-E., and G.M.C.; funding acquisition: grant PI 19/00458 by B.C. and D.R.-A., grant PI 23/01324 by B.C. and F.R.-E., grant BF1-19-13 by B.C., grant PI 016/2019 by B.C., grant CIGC2021 by B.C., and grant ENF22/10 by A.C.-M. All authors have read and agreed to the published version of the manuscript.

Data Availability

All data generated and analyzed during this study are included in this published article.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: One ozone therapy device used in this study (Ozonosan Alpha-plus®) was provided by Renate Viebahn (Hänsler GmbH, Iffezheim, Germany). The use of the other ozone therapy device in this study (Ozonobaric-P, SEDECAL, Madrid, Spain) was supported by a grant (COV20/00702) from the Instituto de Salud Carlos III (Spanish Ministry of Science and Innovation, Madrid, Spain). In 2023, B.C. received financial

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The authors declare no other potential conflict of interest, others than those described above.
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare that the funders had no role in the design of the study, in the collection, analyses, or interpretation of data; nor in the writing of the manuscript; nor in the decision to publish the results. All authors confirm that they had full access to all data in the study and accept responsibility for submitting them for publication.

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Informed Consent Statement

Informed written consent was obtained from all patients involved in the study.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Provincial Research Ethics Committee of Las Palmas, Spain, (protocol code 2019-288-1, approved on May 23, 2019).

Consent for Publication

Not applicable.

ORCID iDs

Bernardino Clavo https://orcid.org/0000-0003-2522-1064
Mario Federico https://orcid.org/0000-0002-6184-9070

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