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Effects of ozone treatment on chemotherapy-induced peripheral neuropathy: a promising research area

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Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of chemotherapy (CT), which involves mainly platinum-derived drugs, taxanes, vinca alkaloids, and proteasome inhibitors. The usual symptoms of CIPN are numbness and tingling, hypoesthesia or allodynia, pain, loss of strength, and alterations in proprioception or thermal sensitivity. CIPN can become chronic, persist for months or years after completing CT, and be associated with and worsen other symptoms, such as anxiety, depression, insomnia, and fatigue. CIPN affects the ability to carry out activities of daily living and markedly reduces patients' health-related quality of life (HRQOL).[1,2] When CIPN occurs during treatment, it can lead to a decreased CT dose or even premature withdrawal, with a subsequent negative impact on cancer prognosis.

Current status of CIPN: Unfortunately, prophylactic and therapeutic measures for managing CIPN are very limited in number and degree of effectiveness.[1] Duloxetine is the only evidence-based treatment, but only for "pain" management, with a "moderate degree" of recommendation, given the "modest magnitude of its benefit.[1]" In a large randomized controlled trial (RCT), compared with the placebo group (0.34), duloxetine provided a pain reduction of 1.06 points on a 10-point scale (using the Brief Pain Inventory-Short Form "average pain"), which disappeared 1 week after stopping the treatment, and it is a treatment associated with potential side effects.[3] Although multiple treatments are usually administered for the management of numbness and tingling secondary to CIPN (such as venlafaxine, oxcarbazepine, amitriptyline, gabapentin, pregabalin, serotonin-norepinephrine reuptake inhibitors, and several antioxidants), the Clinical Guideline of the American Society of Medical Oncology established that there is insufficient evidence to recommend its use outside of RCTs.[1] Moreover, the development and evaluation of new strategies to mitigate and manage the chronic side effects of cancer treatments (CIPN included) was established as an area of urgent research by the American Society of Medical Oncology.[4]

The pathogenesis of CIPN is multifactorial, and different combinations of factors are likely predominant for different drugs. Alterations have been described in the following aspects: i) microtubule activity; ii) ion channel activity (Na, K, Ca, transient receptor potential channels); iii) DNA (with subsequent alterations and dysregulation of intracellular transcriptional and signaling pathways, particularly those associated with DNA repair and apoptosis); iv) mitochondrial functions and cellular metabolism (with a local increase in oxidative stress and scavenger alterations); v) local alterations in the immune system (with local processes of neuroinflammation and microischemia); and vi) myelin alterations and axonal degeneration.[2,5]

Ozone (O_3) treatment (O_3T): O_3 is a highly reactive compound composed of three oxygen (O_2) atoms with higher oxidizing power than O_2, meaning that it can chemically react with different substances by adding an atom of oxygen (or removing electrons) to its molecular structure. Because its oxidizing properties produce lung toxicity, O_3T must always be carried out to avoid airway exposure to O_3.[6]

Medical O_3 is produced from medical-grade O_2 using certified medical O_3 generators. Its clinical use is based on an O_3/O_2 mixture at different concentrations, where O_2 continues to be the most frequent component of the mixture (95–99%), with only a small percentage of O_3 (< 1–5%). Owing to its short half-life (approximately 25 minutes at 30°C), the O_3/O_2 gas mixture cannot be encapsulated or stored and must be produced and administered *in situ*.

The two main routes of O_3/O_2 administration that induce systemic effects are autohemotherapy and rectal insufflation. Using any of those approaches, O_3T can produce an indirect systemic effect by inducing an adaptive response of the tissue and organism. O_3 does not bind to specific receptors, nor does it follow the usual principles of pharmacology: it does not circulate through the bloodstream, nor does it follow the processes of distribution, metabolism or elimination.

At adequate concentrations and for administration, O_3/O_2 interacts with the mucosa of the colon and rectum (rectal route) or with blood components (intravenous route). This produces rapid, moderate, and "controlled" oxidative stress at the local level, especially through interactions with double bonds in unsaturated fatty acids, with the disappearance of O_3 and the generation of O_3 peroxides i) intracellularly, with further actions as second messengers, and ii) extracellularly, as alkenals (mainly 4-hydroxynonenal), which can reach distant tissues through the bloodstream. These second messengers can modulate the glutathione redox system and activate nuclear transcription factors such as nuclear factor (erythroid-derived 2)-like 2, which induces the transcription of antioxidant response elements and the subsequent increase in antioxidant enzymes. Furthermore, at moderate O_3 concentrations, nuclear factor (erythroid-derived 2)-like 2 can also induce a decrease in the activity of Nfkb (nuclear factor kappa B, with proinflammatory action), which is one of the immune pathways modulated by O_3T and leads to anti-inflammatory action. Additionally, O_3/O_2 can induce the activation of glucose-6-phosphate dehydrogenase metabolism in red blood cells (with a further increase in 2,3-diphosphoglycerate and a shift to the right of the oxy-hemoglobin dissociation curve) as well as nitric oxide liberation by the microvasculature, with potential improvements in oxygen delivery to tissues and blood flow, respectively.[6]

In this way, O_3/O_2 can facilitate local autoregulation of ischemia, oxidative stress, and inflammation, with potential beneficial effects on diseases mediated by factors such as chronic ischemic diseases or inflammatory diseases. In the same way, these potential effects of O_3/O_2 look promising against some of the mechanisms involved in the production of CIPN that we have mentioned above. Two reviews have described the potential mechanisms of action and potential role of O_3T in CIPN.[5,7] Additionally, the potential role of the gut microbiota in CIPN has also been suggested, which could offer another potential target for the mechanism of action of O_3T.

Experience in O_3T of CIPN: Because of the limited therapeutic options available for CIPN, treatments are usually offered to patients based on their mechanisms of action or their usefulness in other similar conditions, even if they have not proven effective in CIPN. With the same approach, according to the mechanisms of action of O_3/O_2,

our multidisciplinary chronic pain unit offers O_3T for the management of patients when symptoms are refractory to usual treatments, do not have effective treatment, or conventional treatment is potentially associated with high morbidity. In our hospital, the compassionate use of the O_3T approach was approved by the Health Care Ethics Committee (September 20, 2017). This decision was based on the 37th Article of the World Medical Association *Declaration of Helsinki* (Fortaleza 2013). Currently, in our center, O_3T is prospectively evaluated with the approval of the Ethics Committee of Las Palmas (April 29, 2022), which is registered in the Spanish Clinical Studies Registry (REEC 0063-2022-OBS) and ClinicalTrials.org (NCT05417737).

Therefore, our current experience with O_3T in CIPN patients is focused on different symptoms associated with CIPN and is based on compassionate use in a limited number of patients, pending subsequent evaluation in RCTs. The next paragraphs describe our main preliminary findings using O_3T in CIPN. (Further details are shown in **Additional Table 1**.)

The first report[8] assessed 11 different locations (four hands and seven feet) in a group of seven patients with chronic pain secondary to CIPN (median age of 49 years, range: 36–73 years). Before submission for compassionate O_3T, patients' symptoms were under unsuccessful treatment for a median time of 12 months. Rectal O_3T provided significant and clinically relevant pain relief. A decrease in pain was reported by 86% of the patients. According to the visual analog scale (VAS), the pain level significantly decreased at the end of O_3T (VAS score from 7 to 4) and remained significantly reduced 3 months (VAS score: 5.5) and 6 months (VAS score: 6) after the end of O_3T. This long-lasting effect of O_3T in CIPN pain is consistent with the protracted effect described in the management of some radiation-induced toxicities.[9] The initial magnitude of the effect on the VAS score (3 points on a 10-point scale) and duration of improvement (6 months) compared favorably with those described for duloxetine (a 1-point decrease in a 10-point scale that disappeared 1 week after the end of duloxetine treatment) (**Figure 1**).

The second report[10] described 26 cancer survivors treated with rectal O_3T because of persistent or refractory side effects of cancer treatment. The analysis of the subgroup of 15 patients with CIPN revealed statistically significant improvements in all five domains of the EQ-5D-5 L HRQOL questionnaire (developed by the EuroQol Group), which includes mobility, self-care capacity, ability to carry out activities of daily living, pain/discomfort, and anxiety/depression. The median value of the self-evaluation of health status (EQ-VAS) included in the EQ-5D-5 L questionnaire (from 0 (worse) to 100 (better)) also significantly improved after O_3T (from 50 to 75). Additionally, after O_3T, there was a significant improvement in the grade of CIPN toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE v.5.0) scale of the National Cancer Institute of EEUU. This work revealed that O_3T could improve CIPN toxicity, and patients positively evaluated the impact of O_3T on their HRQOL (**Figure 1**).

A final report in 2023[11] specifically evaluated the impact of O_3T on anxiety and depression in 16 patients treated because of refractory symptoms of severe diseases, most of which were secondary to CIPN. In this work, after O_3T, patients reported a significant improvement in i) the anxiety/depression dimension of the general EQ-5D-5 L questionnaire and ii) both subscales (anxiety and depression) of the focused Hospital Anxiety and Depression Scale. Both subscales of the Hospital Anxiety and Depression Scale were significantly i) correlated with the anxiety/depression dimension of the EQ-5D-5 L questionnaire and ii) inversely correlated with self perceived health status. However, in this study, it was not possible to determine whether the improvement in anxiety and depression was a direct effect of O_3T or if it was partially related to the improvement in physical symptoms reported by most of the patients.

In the complementary management of these patients, O_3T was planned by rectal insufflation, 40 sessions in 4 months. Initial pharmacological treatments were maintained during O_3T and were further reduced or removed in many patients when clinically indicated. Rectal insufflation of O_3/O_2 was well tolerated. The main side effects of O_3T were soft and transient meteorism and bowel bloating, as expected with this O_3T approach. The mild side effects of the procedure were described in our different manuscripts and are consistent with large reviews.[12]

In these works, many patients receiving O_3T also reported improvements in different symptoms associated with CIPN, such as numbness and tingling, and alterations in hand and foot proprioception, a sense of balance, thermal sensitivity, or desire and sexual potency. However, these are encouraging but unpublished data, and they are currently under evaluation.

These reports evaluated patients with refractory symptoms of CIPN after many months (median more than 12 months) of conventional management and revealed relevant clinical improvement (in magnitude and duration) after 4 months of O_3T. These findings are encouraging and merit further research in a clinical condition (CIPN) without established therapy, except for the described effect of duloxetine on painful CIPN. However, these preliminary studies have two notable limitations: they were non-RCTs and had small sample sizes. Therefore, the results must be evaluated with caution. Focused RCTs are needed to validate these preliminary results.

Currently, our hospital is carrying out two related RCTs in patients with CIPN: i) one focused on "pain" (EU CT ID: 2024-518021-16-00, NCT04299893) and ii) another ongoing RCT focused on "numbness and tingling" (EU CT ID: 2024–517196–20–00 and NCT06706544). Additionally, a prospective study is evaluating the impact of O_3T on HRQOL, anxiety, and depression in cancer and noncancer patients treated with symptomatic and compassionate intention (AEMPS/REEC: 0063-2022-OBS, NCT05417737) in our chronic pain unit. Multicenter collaboration could facilitate and accelerate these advances and further research.

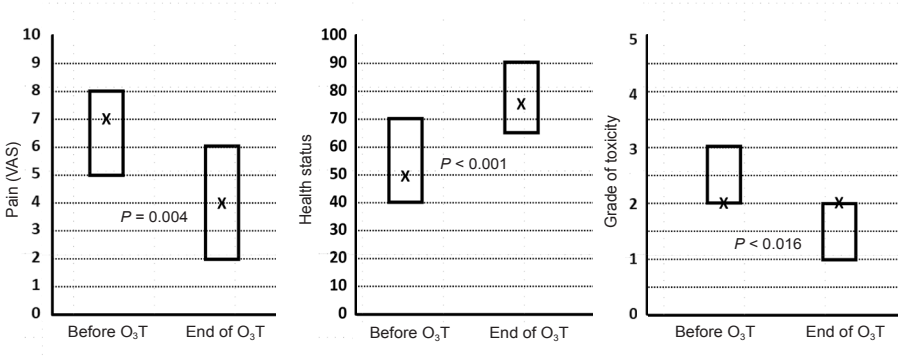

Figure 1 | **Chemotherapy-induced peripheral neuropathy (CIPN): clinical changes at the end of O_3T.**
Clinical details before O_3T and at the end of O_3T: i) Pain, assessed by the visual analog scale (VAS), from 0 (better) to 10 (worse); ii) Health status (EQ-VAS) included in the EQ-5D-5 L questionnaire, from 0 (worse) to 100 (better); and iii) Grade of toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE v.5.0) scale of the National Cancer Institute of EEUU, from 0 (no toxicity) to 5 (death). *P* value of paired comparisons according to the exact (significance) Wilcoxon rank test. Box: Quartiles 1 and 3; O_3T: ozone treatment; X: median value.

Conclusion: CIPN is a common side effect of CT, with a potentially high impact on the administration of CT and the HRQOL of patients. Except for the small benefit of duloxetine for pain related to CIPN, there are limited therapeutic options for the different symptoms associated with CIPN. Few preliminary reports suggest that O_3T could offer clinically relevant improvements in different symptoms associated with CIPN. The magnitude and duration of these results merit further focused research. RCTs are ongoing.

This manuscript, the studies described, and the ongoing trials were partially supported by grants (PI 19/00458 and PI 23/01324) from the Instituto de Salud Carlos III (Spanish Ministry of Science and Innovation, Madrid, Spain, and European Regional Development Fund—ERDF); a grant (PI 016/2019) from the Fundación DISA (Las Palmas, Spain); a grant (BF1-19-13) from the Fundación Española del Dolor (Spanish Pain Foundation, Madrid, Spain); a grant I42/20 from the Colegio Oficial de Médicos de Las Palmas (Las Palmas, Spain); a grant (CIGC'21, CIGC'23-24) from the Cabildo de Gran Canaria (Las Palmas, Spain); and a grant (ENF22/10) from the Fundación Canaria Instituto Investigación Sanitaria de Canarias -FIISC-, (Las Palmas, Spain). One of the two ozone therapy devices used 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).

During this work, SCR was funded by a postdoctoral grant Margarita Salas from the Ministerio de Universidades, Fondos Next Generation EU, and Universidad de la Laguna (UNI/551/2021).

The use of the EQ-5D-5L™ questionnaire by our group was approved (ID 45255) by the ©EuroQol Research Foundation. EQ-5D™ is a trademark of the EuroQol Research Foundation.

One of the two ozone therapy devices used in this study (Ozonosan Alpha-plus®) was provided by Hänsler Medical GmbH (Iffezheim, Germany).

In 2023, BC received financial support for a European grant application from Hänsler Medical GmbH (Iffezheim, Germany).

The authors declare that the research was conducted in the absence of any other commercial or financial relationships that could be construed as potential conflicts of interest.

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Date of submission: August 23, 2024
Date of decision: Ocotber 11, 2024
Date of acceptance: Ocotber 31, 2024
Date of web publication: January 18, 2025

https://doi.org/10.4103/mgr.MEDGASRES-D-24-00074
How to cite this article: *Clavo B, Cánovas-Molina A, García-Lourve C, Cazorla-Rivero S, Federico M, Rodríguez-Esparragón F. Effects of ozone treatment on chemotherapy-induced peripheral neuropathy: a promising research area. Med Gas Res. 2025;15(2):195-197.*

Additional file:
Additional Table 1: *Details of the main results of the studies on O_3T in patients with CIPN.*

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