Ozone Therapy

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ozone therapy can induce an adaptive antioxidant and anti-inflammatory response, which could be potentially useful in the management of chemotherapy-induced peripheral neuropathy.

Keywords: antioxidants ; cancer treatment ; chemotherapy-induced peripheral neuropathy ; chemotherapy-induced side effects ; chemotherapy-induced toxicity ; oxaliplatin ; free radicals ; oxidative stress ; ozone therapy ; randomized clinical trial

1. Introduction

Due to advances in cancer treatment, the number of cancer survivors is increasing, and they are living longer and/or with better quality of life. However, as a consequence, the number of survivors with acute and/or chronic side effects of cancer treatments is also increasing. Development and assessment strategies to mitigate and manage chronic toxicities associated with cancer treatment have been established as an urgent area of research for the American Society of Clinical Oncology (ASCO) [1].

One of the most relevant cancer treatment toxicities is chemotherapy-induced peripheral neuropathy (CIPN), which can produce local alterations (dysesthesias and/or pain) and associated worsening of general symptoms (i.e., anxiety, depression, insomnia, fatigue), with high impact on patients' quality of life. During cancer treatment, the relevance of these symptoms can reduce or delay the scheduled doses of chemotherapy, or even lead to its interruption, with the subsequent decrease in anti-tumoral efficacy. Between 19% and 85% of cancer patients treated with neurotoxic chemotherapy can develop CIPN, and 70–100% in platinum-based drugs [2]. This percentage could be increased by antiangiogenic drugs added to the new chemotherapy protocols [3]. Between 20% and 40% of these cancer patients could suffer pain secondary to CIPN [4]. Unfortunately, the approaches used for the management of other neuropathic pain syndromes do not work properly in CIPN [5] and there are no clinically relevant prophylactic or treatment approaches for CIPN [6][7][8].

The induction of reactive oxygen species (ROS) by chemotherapy drugs, with further oxidative stress (OS), is one of the potential pathogenic mechanisms that can induce CIPN [9], and this work is focused on this mechanism. However, there are other potential mechanisms of the induction of CIPN, many of which are highly related to OS, such as: damage in microtubules, myelin or DNA; local processes of inflammation, ischemia, or ion channel alterations in Na, K, or Ca; and transient receptor potential (TRP) channels [2][10], which show sensitivity to different endogenous molecules, including ROS [11].

In addition to many different approaches, anti-inflammatory drugs and several antioxidant therapies have been evaluated in the management of CIPN, although without conclusive results to date. Therefore, prophylactic and therapeutic options continue to be highly limited in number and efficacy [6][7][8].

The appropriate systemic administration of ozone has been well described as a potential inducer of an adaptive antioxidant response, with the further modulation of OS and inflammation related to several conditions and drugs, including chemotherapy drugs [12].

2. Ozone Therapy in Chemotherapy-Induced Neurologic Symptoms and CIPN

Ozone therapy can induce an adaptive modulation against OS, inflammation, and ischemia/hypoxia. This bodes well for a potential beneficial effect of ozone in CIPN when these mechanisms are involved. Recently, we summarized the main experimental research describing the potential of ozone treatment to prevent or treat several chemotherapy-induced side effects [12]. However, research focused on chemotherapy-induced neurologic complications or CIPN are even less common. Here, we describe a few relevant related studies that offer potential support for further research about ozone in CIPN.

An experimental study evaluated rats intraperitoneally injected with 5 mg/kg/day cisplatin for 3 days to produce cisplatin-induced ototoxicity, which was confirmed by test with distortion product otoacoustic emissions. Rats were randomized to (1) no treatment (control group); (2) ozone by “rectal” insufflation; (3) ozone by “rectal + intratympanic” insufflation. Rectal and intratympanic insufflations consisted of 2.3–3 mL of O_3/O_2 gas at a concentration of 60 µg/mL administered once per day for 7 days. Ototoxicity was significantly lower ($p < 0.05$) in ozone groups than the control group, with (1) partial recovery of audition and lower distortion of product otoacoustic emissions, and (2) lower histopathological damage in the outer hair cell of the inner ears. However, the addition of intratympanic insufflation did not provide further benefit when compared with rectal insufflation of ozone alone [13].

A study on rats assessed the effect of ozone in drug-induced diabetic neuropathy. Four weeks after the induction of diabetes by a single intraperitoneal injection of streptozotocin, the right sciatic nerves were removed. Compared with the “diabetic group without ozone and without insulin”, the diabetic groups treated with ozone, or with insulin, or with ozone + insulin, showed higher amplitudes of conduction velocity and compound action potential, higher total antioxidant status, lower total oxidative status, and lower OS index. Thus, this study showed that ozone treatment partially prevented drug-induced neuropathy, and this effect was mediated by modulation of OS [14].

It has been also described that ozone can offer neuroprotective effects after an injury of cutting of the sciatic nerve. In a large experimental study with one hundred rats, a transverse cut injury to the sciatic nerve was produced, with further reparation of nerve stumps. Compared with the group without ozone treatment, the group with two months of intraperitoneal ozone treatment (5 mL at a concentration of 35–40 µg/mL) showed more myelinated nerve fibers under electron microscopy, and an increase in plasma antioxidants (SOD, CAT, GSH-Px). Although the pathogenic mechanism in this study was not drug-induced, and could not be directly applicable for CIPN, we believe it is of interest to note the described enhancement of damaged-nerve regeneration by ozone treatment [15].

Finally, we describe our experience in a small group of patients with chronic neuropathic pelvic pain secondary to cancer treatments (chemotherapy, radiotherapy, and surgery) [16][17]. In this group, cancer treatment included radiotherapy in five patients, chemotherapy in four, and surgery in two. There was complete tumor response after cancer treatment, but patients experienced refractory chronic pelvic pain after several months of conventional treatments. Pain level, according to the Visual Analog Scale (VAS) was 7.8 ± 2.1 before the commencement of ozone therapy by local and rectal insufflation. There was a significative ($p < 0.05$) and clinically relevant decrease (>5 points in VAS) pain reduction after the first three months of ozone treatment [16], at the end of treatment, and nine months after the end of ozone therapy. Five of six patients were able to decrease or even discontinue analgesic intake requirements [17].

3. Conclusions

CIPN is a common side effect of cancer treatment with a potential impact on the success of the oncologic therapy and a high impact on the quality of life of patients. There is no evidence of clinically relevant prophylactic or therapeutic approaches. Further research is required to better understand the role of OS in CIPN and the clinical role of its modulation. Appropriate use of ozone is an effective adjuvant therapy that can modulate OS, although randomized clinical trials are urgently required to establish its potential benefit in CIPN. A related trial is ongoing.

References

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