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Title: Ozone Therapy as Adjuvant in Oncology

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1. Title ISCO3/CLI/00/14. Ozone Therapy as adjuvant in Oncology.

1.1. Brief background

Cancer is one of the leading causes of mortality worldwide. Radiotherapy and chemotherapy are meant to kill tumour cells by different mechanisms, however the therapeutic effect of both is mediated by the intracellular increase of free radicals. Free radicals can also accumulate in healthy cells, causing oxidative stress, which usually leads to unintended damage in healthy tissues. Historically, efforts to prevent or treat many of these side effects has been limited. There is accumulating evidence that medical ozone therapy can induce a low level controlled oxidative stress, which is then able to stimulate an adaptive antioxidant response in healthy tissue, thus preconditioning the whole body for what is to come.[1]

Over several decades, prestigious journals have published articles on the capacity of Ozone (O_3) to induce direct damage on tumor cells and, as well, to "theoretically" promote the effects of radiotherapy (RT) and chemotherapy (CT).[2] Hence, many clinicians advocate their use in cancer treatment. However, these studies have been conducted *in vitro* in the laboratory and in some animal models.[3,4] As such, the direct effect of O_3 on tumor cells have been demonstrated in very different conditions to those employed in clinical Ozone therapy sessions. In clinical practice, usually the O_3 does not enter into direct contact with the tumor cells i.e. the O_3 does not exercise a direct effect but its multiple effects are, in reality, mediated by secondary messengers (such as H_2O_2 and 4-hydroxynonenal). [5,6] Apart from this "indirect mechanism of action" O_3 stimulates adaptive mechanisms that can induce modulations in the organism on: immune system, blood flow and oxygenation and oxidative stress. These "indirect effects" can be, as well, potentially beneficial in anti-cancer therapy, as has been suggested by some studies.

Verifying medical ozone therapy as an adjuvant in oncology can only be established via clinical trials specifically directed towards specific tumours, and in well-defined circumstances such as tumour status and background characteristics of the patients. Unfortunately, the ability to perform such studies has been limited. Nevertheless, recent preliminary clinical trials support the benefits of a complementary treatment of medical ozone as support and palliative therapy in oncology, particular in the treatment of side effect of complications related with chemotherapy or radio therapy.[7-12]

Complementary treatment with ozone therapy to mitigate side effects, during chemotherapy and/or radiotherapy, should be done in coordination with the oncologist who administers the treatment to the patient.

1.2. Purpose

The purpose of this SOP is to describe the potential usefulness and methods for medical ozone as adjuvant therapy in oncology. Targeted areas include local wound care from radiation or surgery, mucositis, chemotherapy-induced peripheral neuropathy, and pain.

1.3. Scope

The recommendations suggested here within regarding the various procedures will specify the routes of administration, doses, volume of gas, and frequency of application of ozone in the management of collateral effect of basic therapy of oncology patients.

1.4. Acronyms, abbreviations and definitions

Chemotherapy (CT); GI (Gastro Intestinal); Heme oxygenase-1 (HO-1); Highly ozonated oil (HOO); Intraperitoneal route (IPO_3); Lipoperoxides, (LOP's); Major Autohaemotherapy (MAHT); Minor Autohaemotherapy (MiAHT); Oxygen-Ozone therapy (O_2/O_3); Ozonated Saline Solution (O3SS); Ozone Nanobubble water (ONBW); Peroxide Values (PV); Radiotherapy (RT); Reactive oxygen Species (ROS); Rectal ozone therapy (RIO_3).

2. Responsibility

Nurses	Patient accommodation Preparation of the clinical procedure Supervision of patients, and vital signs control (temperature and pressure) Notification of possible complications
Physician	Medical record and anamnesis Assessment of the indication, contraindications Request the written informed consent and the privacy consent Request labs. test Applications and follow-up Record all data on medical records Reporting any late complications

3. Etiologic

Lesion by radiation oncology

Wound healing in oncology

Pain and side effects of radio and chemotherapy

4. Diagnostic Consideration

Differentiate between symptoms caused by cancer therapies and those from any other cause (prior conditions of known etiologies, pain from old injuries, tumor relapse, or new unrelated issues).

5. Conventional Treatment / Management

Conventional medical literature reflects the need for more comprehensive and effective methods to treat side effects of oncology therapies. Often, treatment plans are stalled or cancelled due to the intolerable side effects. On the other hand, many times, the management of chronic side effects of oncology therapies can be difficult, inexistent, or associated to high morbidity procedures, all of them limiting the quality of life. For these reasons, the American Society of Clinical Oncology (ASCO) established a priority research area to develop novel strategies to mitigate the chronic side effects of cancer therapy.[13]

6. Evidences of ozone effect

According to the Madrid Declaration, the level of evidence rated at Level C (Madrid Declaration ISCO3/QAU/01/03). Level C is defined as being clinically useful but having limited support from conventional trials.

Table 1. Examples of clinical trials using ozone as complementary treatment in oncology.

Number of patients	Condition / Outcome measures	Ozone protocol	Main Results	References
Chemotherapy-induced peripheral neuropathy (CIPN)[14,15]				
42	Brief Pain Inventory-Short Form (BPI-SF)	RiO3. Concentration of O_2/O_3 increasing from 10 to 30 µg/mL	Recruiting	NCT04299893
7	Pain secondary to grade II or III CIPN	RiO3 initial concentration: 10 µg/mL, increased by 5 µg/mL every two sessions until max. of 30 µg/mL, the gas volume started at 180 mL/session and was slowly increased in successive sessions (depending on patient tolerance of bowel bloating) up to max. of 300 mL/session if tolerated	Clinically relevant pain improvement	Bernardino Clavo *et al.* (2022).[10]
Radiation Toxicity - Chemotherapeutic Toxicity				
105	5-level, 5-dimension EuroQol (EQ-5D-5L) questionnaire	Chemotherapy induced Peripheral Neuropathy Delayed Wound Healing	Recruiting	NCT05417737

Number of patients	Condition / Outcome measures	Ozone protocol	Main Results	References
		Chronic Pain Refractory Pain		
26	Side effects of radiotherapy and chemotherapy HRQOL (according to the EQ-5D-5L questionnaire) and grade of toxicity (according to the CTCAE of the National Cancer Institute of EEUU (CTCAE v.5.0)	RiO3, concentrations were progressively increased between 10 and 30 µg/mL. For topical administration, ozone concentrations usually ranged between 40 and 10 µg/mL, according to patients' tolerance or on the basis of the presence or absence of local infection.	Significantly decreased toxicity ($p < 0.001$) and improve the HRQOL	Bernardino Clavo *et al.* (2023).[16]
1	Stage IV rectal adenocarcinoma with liver and lung metastases	RiO3 + Ozonated Olive Oil inhalation (OT combined with PEMF) Rectal route: 8 mg/day, 5 times/week Ozonated Olive Oil: 40 min/day, 5 times/week	Improvement in well-being, autonomy, and pain control, pause in tumor growth despite more than 60 days without using classic treatment. Significant decrease in pain in five of six	Gaspary, J. (2020)[17]
6	Chronic pelvic pain secondary to cancer treatment	RiO3: 180 mL/session at the beginning, increase up to max. of 300 mL/session if tolerated, initial concentration: 10 µg/mL, increased 5 µg/mL every two sessions up to max. of 30 µg/mL	Significant decrease in pain in five of six patients, improvement in associated symptoms (vaginal dryness, hematuria, rectal or vaginal wounds, tenesmus, and the number of bowel movements per day)	Bernardino Clavo *et al.* (2021).[11,18]
62: 35 Control 27 O3	Chemotherapeutic enteritis	MAH	MAH of ozone effectively attenuated chemotherapeutic enteritis and the blood hypercoagulability in patients	Qingqing Yu *et al*. (2020).[19]
83	Oral, breast and brain cancer	CT + MiAH (100 µg) / RiO3 (200 mL at 35 µg/mL), alternatively for 6 weeks till the duration radiotherapy.	Reduce side effects of radiation.	Mili Shah and Arvind Kulkarni (2020).[19]
3	Rheumatologic symptoms, in breast cancer undergoing aromatase-inhibitors therapy.	MAH	Reduce rheumatic symptoms with no side effected	Umberto Tirelli *et al*. (2019).[20]
100: 60 Ozone 40 Control	Chemiotherapy complications during the post-operative period in patients with	O_3SS low dose, 6 sessions	Immune-modulating effect based on the metabolism improvement in immune-competent cells, which	E. Kontorschikova et al. (2019).[21]

Number of patients	Condition / Outcome measures	Ozone protocol	Main Results	References
	onco-gynecological pathology		reinforces their tolerance to the toxicity caused by cytostatic or radial therapy.	
50	Fatigue symptoms	MAH	No side effects were found, and 35 patients (70%) achieved a significant improvement (> 50%) of the symptoms	Umberto Tirelli *et al*. (2018).[9]
5	Glioblastoma	Intra-tumoral	Increased survival rates compared to historical series not treated with O3. The patient treated immediately after the first surgery is alive and without recurrence	Megele R. *et al.* (2018).[22]
12	Persistent Radiation-Induced Rectal Bleeding	RiO3 and/or topical application of ozonized-oil	The median grade of toxicity improved from 3 to 1 ($p <$ 0.001) and the number of endoscopy treatments from 37 to 4 ($p = 0.032$). Hemoglobin levels changed from 11.1 (7–14) g/dL to 13 (10–15) g/dL, before and after ozone therapy, respectively ($p = 0.008$).	Bernardino Clavo *et al.* (2015).[12]
100	Coagulation parameters and postoperative complications rate in colorectal cancer patients	O_3SS	Normalization con coagulation and reduce complication rate from 22 to 14%	Gataullin IG, Frolov SA. (2014)[23]
60: 30 Control 30 Ozone	Breast Cancer-Related Lymphedema	RiO3	Reduce limb volume and thickness	Intsar S. Waked *et al.* (2013).[24]
40: 20 MAH VA CT 20 CT	Lung cancer	CT or CT + Viscum Alba (VA) + O3 (autohemotherapy)	O3 and VA therapy was safe and seems to improve the quality of Life (QLQ30) in advanced lung cancer patients when used in association with CT.	Borreli E. *et al*. (2012)[25]
Mucositis				
Review	Mucositis in patients after head and neck radiotherapy.	Ozonized water	Ozonized water with a concentration of 2-4 ppm for approximately 5 min has the potential to cure oral mucositis.	A. G. Arumsadu *et al*. (2021)[26]
93: 31 OT rinse 1 min 31 OT rinse 3 min 31 No OT	Oral mucositis induced by the treatment of head and neck cancer with radiotherapy.	Ozonized water	Reduce the pain severity and oral mucositis induced by radiotherapy	Farzad Ghorbani *et al*. (2021)[27]
15	Pediatric cancer patients.	Ozonized water	Total remission of mucositis with ozone therapy was achieved at 7 days, in the most severe cases.	L. M. Perla Karina *et al*. (2020)[28]

Number of patients	Condition / Outcome measures	Ozone protocol	Main Results	References
1	Mucositis after chemotherapy and radiotherapy	Ozone in both aqueous and gaseous forms	Improve symptoms and quality of life.	J. E. Shenberg, and C. Blum (2011).[29]

Legend:
CT, Chemiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; HRQOL, Health-Related Quality of Life; MAH, major autohemotherapy; MiAH, minor autohemotherapy; O_3SS, Ozonized Saline Solution; OT, Ozone therapy; PEMF Pulsed Electromagnetic Fields; RiO3, rectal insufflation; VA, Viscum Alba.

7. Procedure

7.1. Inclusion criteria

- Participant is willing and able to give informed consent for ozone treatment
- Male or female, aged >18 years
- Anticipating or suffering side effects of chemotherapy and/or radiation therapy

7.2. Criteria of exclusion

The patient should not be treated with ozone if any of the following conditions are present:

- Female participant who is pregnant, nursing, or planning pregnancy during the course of treatment
- Significant renal or hepatic insufficiency
- Uncontrolled hyperthyroidism
- Abnormal coagulation, thrombocytopenia, active bleeding
- People with allergies or hypersensitivity to medical ozone
- Period of instability of severe cardiovascular diseases
- G6PD [glucose-6-phosphate dehydrogenase deficiency] (favism, actual haemolytic anaemia)
- Hyperthyroidism – Basedow Graves' disease
- Thrombocytopenia (less than 50,000) and serious bleeding disorders
- Acute alcohol intoxication
- Massive and acute bleeding
- Prolonged convulsive states
- Hemochromatosis or severe anaemia
- Patients being treated with copper or iron intravenously
- Any situation that does not allow safe treatment

7.3 Pre-treatment requirements

The practitioner will be well-trained in this method. Fill all medical records of the patient, get the written informed consent (ISCO3/QAU/00/21) and the privacy consent. Make the appropriate diagnoses and consider all indications and contraindications. Define the appropriate protocol matching the severity of the disease, affected area, and patient's condition. Prepare the appropriate dose of ozone using an adequate device (ISCO3/DEV/00/01). Avoid the use of non-recommended way of administration of ozone (ISCO3/LEG/00/10).

7.4 Clinical evaluation

Follow the diagnostic and physical examination criteria to identify the appropriate protocol.

7.5 Indications

7.5.1. Chemotherapy—Induced Mucositis

Mucositis is a painful condition that involves ulcerative lesions in the mucous membranes (mouth and G.I. tract, vaginal, vesical), which develop via oxidative damage to the mucosal cells. It produces pain, function alterations, and affects quality of life as eating, swallowing, and talking become increasingly difficult. In severe cases, the airway mucosa can be compromised, leading to anoxia-induced brain injury and even death.

Mucositis affects up to 90% of patients receiving chemotherapy. The condition is progressive and dose-dependent. The most severe effects are in patients receiving "conditioning therapy" prior to bone marrow transplants, since it weakens the immune system.

Neutropenia and oxidative stress (free radical damage) are the etiological causes of mucositis. Since there are no warning signs as to when this condition may begin during treatment, a preventative ozone protocol is rational, and supported by clinical experience. Once mucositis is clinically obvious, it is more difficult to treat because the oxidative damage is already well advanced, although there are also successful clinical reports with ozone therapy.

Pre-conditioning of the body with ozone *before* initiating chemotherapy, theoretically, could offer the best chance of ameliorating the side effects. Experience confirms that the chemotherapeutic regimen will attain its maximal therapeutic potential because of the oxygenating effect of ozone beforehand.[30,31]

Saliva total antioxidant capacity and status are important indicators of the patient's oral and general oxidative stress condition and could help in treatment planning as well as during treatment.[32,33]

If preconditioning is not feasible however, because the chemoradiation has already begun, the ozone therapist can still work with confidence knowing that ozone still has a high therapeutic potential even in the face of an ongoing oxidative insult.[34]

The following protocols specify the dose of medical ozone in the treatment of the side effects of chemotherapy, radiation, and surgery in oncology. It is important to prevent the early discontinuation or truncation of conventional therapy due to patients' unwillingness or inability to continue, on account of the suffering caused by treatment side effects.

The patient will already be in a state of oxidative stress, with a compromised immune system and increased risk of local and systemic infection. Therefore, it is critical that low concentrations of ozone are initially used, then *slowly* increased over the course of treatment in order to avoid potential toxic effects of ozone. With this in mind we "start low and go slow".[35]

Ozone concentrations are increased by 5 µg per week, up to a maximum of 45 µg/mL. Then the dose is reduced in the same increment while the patient's condition improves. The author's experience is that a prolonged course of regular ozone delivered in pulses, over 2-4 months, gives the best "transient therapeutic shock".

7.6. Recommended protocol, doses, intervals

7.6.1 Potential ozone therapy protocols for the treatment of radiation-induced mucositis

Mucositis in oral, laryngeal, and pharyngeal tissues is an inevitable adverse reaction during radiation therapy. Preconditioning with ozone therapy to upregulate Nrf2 activation of Antioxidant Response Elements (ARE's) has the potential to prevent this adverse effect. Nrf2 inducers, such as ozone, are important for the protection of the upper aerodigestive tract from radiation-induced mucositis as they eliminate ROS and induce keratin layer thickening of the epithelium.[30]

Standard approaches such as improved oral hygiene, immunonutrition, and analgesics are important but have limited efficacy. Tube feeding places a heavy burden on the patient. Within the irradiated fields, bones become hypovascular, hypocellular and hypoxic with minimal ability to resist trauma or be repaired. Because ozone therapy overcomes tissue hypoxia, properly and judiciously administered ozone is an ideal intervention in repairing the undesired damage.

Proposal Protocols:

For the first week treat every day for 5 days utilising Ozonated Saline drips and MAHT. Refer to Table 2 for more specific guidelines.

7.6.1.1 Ozonated Saline Drips

Two sessions of ozonized saline solution (1-2) µg/ kg b.w. in the first week. These are ideal to begin with as they require a smaller intravenous catheter or butterfly needle and allow the ozone therapist to get to know the patient's venous access. Also, as a volume expander it may improve the circulation and facilitate ease of access and establish better blood flow for MAHT. Proximal to radiation wounds, the ozonated saline can be instilled subcutaneously and massaged toward the ulcer or lesion. It can be applied topically, directly over areas of concern.

7.6.1.2 Major autohemotherapy

See Table 2 for specifics on dosing. The bell curve represented in the table, maintains the redox balance and provides a high level of infection control. As per ISCO3 guidelines see (ISCO3/MET/00/01 Major Autohemotherapy).

7.6.1.3 Minor autohemotherapy

MiAHT: 3 times a week or every second day following the same microgram concentration as the MAHT. MiAHT is a strong inducer of heme oxygenase-1 (HO-1) also known as heat shock protein 70. As per ISCO3 guidelines see (ISCO3/MET/00/02 Minor Autohemotherapy).

7.6.1.4 Ozonated oil

Ozonated oil: once radiation has started, the oral administration of ozonated oil is begun. One to 3 mL every 6 h swished around with the tongue to coat all mucosal surfaces. Ozonated oil in gelatin capsules can be swallowed to treat the upper gastrointestinal mucosa and possibly small intestine. Recently is has been reported a preliminary study that shown thta oral administration of ozonized oil represents an integrated approach to decrease the risk of radio-chemoresistance and cancer relapses in cancer patients. [36]

7.6.1.5 Ozonated water

Purified ozonized water 250 mL 2-3 times a day. Make fresh with bi-distilled water by microbubbling ozone through it for 10 min and then drink immediately with a swilling action.[28,37,38] Ozonated Water can be given by enema to treat the colon: 1 – 1 ½ L ozonated bi-distilled water via rectal instillation (10 µg/mL 2 x week). Bi-distilled ozonated water can be instilled into the bladder for radiation induced hematuria at 20-25 µg /mL.[39] Ozonated saline has also shown itself to be effective for this purpose and may only need to be administered once. Ozonated water can be used rinse to treat mucositis.[26,28]

7.6.1.6 Rectal Insufflations

Rectal insufflations can be substituted for intravenous methods from time to time or as necessary if venous access is too difficult or uncomfortable for the patient. As per ISCO3 guidelines see (ISCO3/MET/00/23 Rectal Insufflation). Proposal protocol of RIO3 would be 180 mL/session at the beginning, increase up to max. of 300 mL/session if tolerated, initial concentration: 10 µg/mL, increased 5 µg/mL every two sessions up to max. of 30 µg/mL.

7.6.2 Potential systemic Protocols for the Complementary Use of Ozone in Chemotherapy

Table 2. Proposal protocol for the treatment of chemotherapy induced mucositis.

Method	Concentration of O_3 (µg/mL)	Week	Cumulative number of Treatments	Chemo/Rad Treatments
2xO_3SS* 3xMAHT 2xMiAHT	1-2** 15 15	1	4	Start
3xMAHT 2xMiAHT	20-25 20-25	2	7	Start
3xMAHT 2xMiAHT	25-30 25-30	3	10	Start
3xMAHT 2xMiAHT	30-35 30-35	4	13	Start
3xMAHT 2xMiAHT	35 35	5	16	Start
2xMAHT 2xMiAHT	35 35	6	18	
2xMAHT 2xMiAHT	35 35	7	20	
2xMAHT 2xMiAHT	35 35	8	22	
2xMAHT 2xMiAHT	30 30	9	24	
2xMAHT 2xMiAHT	25 25	10	26	

Note: Avoid chemotherapy and ozone on the same day to avoid interactions between the specific chemotherapeutic drugs and the ozone molecule. Ozone therapies can be given on the same day as radiation therapy.
Legend: O_3SS, Ozonized saline solution; MAHT, Major auto hemotherapy; MiAHT, Minor auto hemotherapy; * O_3SS or MAHT; ** µg/ kg b.w.

More frequent initial treatments are preferable to a one off, if meaningful and continuous improvement is to be achieved. Each visit should include a careful analysis of response to the previous treatments, so that optimal and effective future dosing can be carried out.

By starting with ozonated saline, we ensure a low ozone dose, and we also volume expand the patient. In addition, infusion is more comfortable with a smaller gauge intravenous needle or cannula (23 G). Over the sessions, the patient's venous access becomes more familiar to the ozone therapist. If venous access proves impossible, a small volume of ozonated saline may be painlessly instilled subcutaneously and massaged away to keep the swelling to a minimum.

In the case of patients treated with chemotherapy, who require several treatment cycles, the venous approach can be complicated, so the route of choice to supply ozone would be the rectal route. See 7.6.1.6.

7.6.2.1. Ozonated Water

Ozonated water can be produced in strengths ranging from low concentration (1-3 µg/mL), medium (4-8 mg/L) and high (10 - 25 mg/mL). The choice of concentration and application frequency will take into account the clinical case status. Bi-distilled, distilled and purified deionized water can be used to prepare ozonated water.

As mentioned earlier, systemic and local ozone therapy pre-conditioning can be advantageous and reduce undesirable side effects. Ozonated water at medium concentration can be used as a mouthwash before, during and after chemotherapy sessions.

In severely infected cases, swish the oral mucosa with 50 mL at high ozonated water concentration for 30 s. Repeat with another 50 mL and gargle the posterior portion of the oral cavity. Repeat three to four times per day. Reduce usage frequency and concentration according to healing phase. In moderate, non-infected cases, follow the same steps using a medium ozonated water concentration.

Even though drinking ozonated water might be safe and effective, but due to the lack of scientific evidence, we cannot recommend drinking ozonated water. As for swallowing ozonated water after its use as a mouthwash for 30 s, we doubt there would be enough residual ozone in the water and have beneficial effect when swallowed. [28,37,40,41]

7.6.2.2. Ozonated Oil

Ozonated oil (1-3) mL of Peroxide Values (PV) 400-600, 3 applications per day. Ozonated oil is ideally purchased from a laboratory that has robust ozonating equipment and quality control facilities to quality e reliable PV. Swill around all mucosal surfaces with the tongue; hold until swallowed.[36,42]

In case of ozone toxicity, use the procedure described in ISCO3/CLI/00/01. For any side effect use the forms ISCO3/REC/00/03. Use ozonized oil of know peroxide index ISCO3/LAB/00/04 and subjected to appropriate quality control.[43]

7.6.3 Potential ozone therapy protocols for the treatment of Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy is caused by oxidative stress leading to inflammation, hypoxia, and ischaemia. This condition can be very painful and/or produces numbness, burning, hypoesthesia, and tingling in the hands and feet. The judicious use of ozone under the correct concentration produces an effect similar to preconditioning. This is achieved indirectly through secondary messengers as there are no ozone receptors in the human body.

Through these early (ROS) and late phase (LOP's) biochemical reactions, a well-known analgesic effect is achieved. In the peripheral nervous system, endorphins are released that block the transmission of pain signals to the higher centres. Similarly, local transforaminal injections achieve central nervous system release of enkaphalins via the interneurons which produce central analgesia. There are clinical reports, refers that this analgesic response is attained very quickly after injections and is well maintained over time.[10,44]

If ozone therapy is used, it could be suggested (based on animal studies)[45-47] the precondition of patient with ozone to avoid the oxidative damage caused by chemotherapy.[48] Then intersperse the ozone treatments before, during, and after the chemotherapy cycles. Avoid doing both chemotherapy and ozone on the same day so as to avoid direct interactions.

7.6.3.1 Glove Technique

Glove technique: Slowly infiltrate ozone gas [1/4" 30 G needle; 5-15 µg/mL x 10-20 mL] subcutaneously on the dorsum of the hand or foot and massage down into the distal extremities of the digits [every day for 5 days, then 2 times per week for one month].

7.6.3.2 Major autohemotherapy

See Table 2 for specifics on dosing. Use MAHT 3 times a week. The bell curve represented in the table, maintains the redox balance and provides a high level of infection control. As per ISCO3 guidelines see (ISCO3/MET/00/01 Major Autohemotherapy).

7.6.3.3 Rectal Insufflations

Rectal insufflations can be an alternative for intravenous methods from time to time or as necessary if venous access is too difficult or uncomfortable for the patient. Use (10-35 µg/mL x 300 mL, 3-5 times a week can be substituted for autohemotherapies if venous access is poor. As per ISCO3 guidelines see (ISCO3/MET/00/23 Rectal Insufflation).

7.6.3.4 Ozonated oil

Rubbed into hands Ozonated Oil and feet 1-2 times a day.

7.6.3.5 Ozone infiltrations

Ozone infiltrations to nerve roots [dorsal horn afferent] at lumbar [10-15 µg x 5-10 mL] and cervical spinal segments [1-3 mL].

7.6.3.6 Limb bagging

Limb Bagging – Wet the area to be treated and remove any dead, loose, and nontender skin without causing trauma. Be sure the bag is well sealed at the open end and that there is a second tube flowing excess gas to a destructor unit. The concentration should be in the range of 10-20

µg/mL and administered for 15 min. Daily for first week then 1-3 times a week for one month. [ISCO3/MET/00/10 Gasification in Plastic Bag].

7.6.3.7 Tender points injections

When treating peripheral neuropathy caused by chemotherapy, it is important to first trace back to the spinal segment and treat any nerve compression that could potentially be inhibiting nerve conduction (e.g.: disc herniation, arthropathy of knee or elbow, impaired circulation, radiculopathy, misaligned vertebrae, sciatica, and similar impediments). Inject tender **Biologically Active Points** with 5-15 µg/mL of ozone per 1-10 mL. The idea is to treat the whole limb and not just the localized peripheral neuropathy.

7.6.3.8 Other Naturopathic Procedures

Additional Naturopathic Care might include: **Hot and Cold foot and hand baths** – 2 times a day for the first week then 2-3 times a week for one month. Hot for 5 min at 40-48 ˚C (105-120) ˚F followed by cold for one minute at 7-15 ˚C (45-60) ˚F for one minute. Repeat this sequence three times in any given session.[49] Improves circulation and lymph flow to and from affected areas. Has a very soothing and calming effect on the patient.

Consider **SCENAR**, **TENS** unit or **Cellsonic** electric stimulation to rectify imbalances in nerve conduction as all three techniques re-establish healthy membrane voltage potentials.[50,51]

7.6.3.9 Wound Healing after Cancer Surgery

Presentation of post-surgical cancer wounds that are not closing are usually caused by infection or ischaemia/hypoxia. For wounds to heal following surgery, an adequate delivery of oxygen through the microcirculation is critical, as oxygen plays a crucial role in collagen formation, new capillary growth, and the control of infection.

Basic scientific studies have clarified that healthy blood flow and oxygen are the main factors for the regeneration of damaged tissues through granulation.[52]

7.6.3.9.1 Infected Wounds

Inject around and beneath the infected site staying away from the inflamed and damaged central lesion. Inject outside the "zone of rubor". Keep injecting as the needle is withdrawn until it exits the epidermis. If a lot of injections are needed, it is easier to fan out from one entry point than to make multiple injection sites. Get good coverage around the wound, and from deep to superficial. Stronger ozone (20-30 µg/mL) is required for infection control, after which lower concentrations (5-15 µg/mL) can be used for healing (the now uninfected wound). Inject around the wound every day until the infection is resolved, then 1-3 times per week until healed by granulation (second intention).

Ozonated oil: Place in the wound sulcus once a day, ozonized oil PV 600-800.

Ozonated water: Aqueous ozone acts as a powerful disinfectant which controls bleeding and cleanses wounds in bones and soft tissue. It improves healing by increasing the local supply of oxygen to the wound area. It facilitates the metabolic processes related to wound healing. Ozonated water increases the temperature in the wound area.

Cupping: The raw ozone gas can be applied over the wound for debridement and infection control [30-40 µg/mL] or to promote healing [10-20 µg/mL] for 15 min once a day.

7.6.3.9.2 Uninfected Non-Healing Wounds

Due to hypoxia: Low ozone concentration (5-15 µg/mL) can be injected around and under the wound to promote granulation and healing by second intention. O3SS and/or MAHT 3 times a week for 4 weeks to maintain oxygen saturation of the wound site. The penetration of the ozone injections needs to be deep so that we don't just get surface closure whilst leaving a non-approximated pocket underneath. Ozone oil gel can be placed in the open sulcus once daily.

Scars (Cicatrices): from breast mastectomy and other surgeries, the scars can be painful or uncomfortable and resist full range of body mechanics. Ozone 5 µg/mL (25 or 30 G needle) infused along the central midline of the scar will separate the layers of fascia and improve the flexibility. Scars soften and become less red. Frequency recommended is 1-2 times per week for 3-4 weeks.

7.6.3.10 Radiation Wounds

Systemic Ozone therapies (as per Mucositis protocol in Table 2) supported by local injections, ozonated oil, and ozonated water applications.

Local Injections: inject slowly under and around the lesion, entering the skin just outside the affected (Rubor) zone. One-5 µg/ml x 10-20 mL. Every day x 5 days then 2-3 x week for a month then 2 x month for maintenance.

Ozonated Oil: Apply to wound and associated skin changes 2 x day. PV 400-600.

Ozonated Water: Bi-distilled ozonated water (concentration: 20 µg/mL, bubbled for 10 min) to lavage and debride the wound and to prepare it for ozone bagging (or cupping).

Ozone Bagging (cupping): 15 minutes followed by ozone water compress application.

Alternative topical-only protocol

In Tomsk, Russia, a topical protocol has been worked out which doesn't necessitate any of the more invasive systemic methods.

Reproduced by permission of the author (modified the topic concert the use of ozonized oil):

1. Ozonate 100 mL of distilled water for 5 min with an ozone concentration of 5-10 µg/mL (5 -10 mg/L).

2. Next, wash the wound with ozonated water before bagging it for 10-15 min using ozone concentration 10 µg/mL.
3. A compress using ozonated water is then applied on the skin around the border of the wound.
4. Patients use the ozonated oil (PV 400-600) at home 1-2 x/day for a month. There are 3-5 treatments per week for up to 10-15 days, followed by a break of 5-7 days. Patients have 2-3 rounds of treatments.

Effects: Ulcer detersion (cleansing and debridement) from purulent deposits, active regeneration and healing of the ulcerous skin defect.[38,53] With this protocol, it is very likely that continuous, rapid improvement will be noted.

7.6.4 Fatigue, hair loss, insomnia, pain

For any of the other side effects of chemo-radiation not mentioned here, it should be considered that ozone therapy administered for any of the chemotherapy or radiation side effects will thereby also address fatigue, insomnia, and pain.

For hair loss, ozone gas is infused under the scalp with a 30 G needle at 10-15 µg/mL and massaged to disperse evenly. The gas could also be applied topically in a similar fashion to limb bagging, using a modified shower cap.
The intraperitoneal route has shown promising results in pain management refractory to all other methods[54] but requires special training to perform. Up-to now is considering a non-recommended way of administration of ozone (ISCO3/LEG/00/10).

Fatigue may be caused by all cancer treatments due to tissue damage or tumour lysis syndrome. There is usually massive production of dead cellular debris that must be removed. Ozone is a valid adjunctive therapy for fatigue in cancer patients.[9]

7.7 Patient Follow-up

Daily at first then 2 times per week. Continue maintenance treatments as required.

8. Contingencies; Corrective Actions

In case of incidental O_3 inhalation follow procedure ISCO3/CLI/00/01.

9. References

9.1 SOP References

ISCO3/QAU/00/21. Informed Consent Form in Ozone Therapy.
ISCO3/MET/00/23 Rectal insufflation

ISCO3/DEV/00/01 Guidelines and Recommendations for Medical Professionals Planning to Acquire a Medical Ozone Generator.
ISCO3/CLI/00/01. First Aid in ozone therapy (Inhalatory exposition and accidental over dose)
ISCO3/MET/00/01 Major Autohemotherapy (2016)
ISCO3/MET/00/02 Minor Autohemotherapy (2016)
ISCO3/REC/00/03 The ISCO3 Safety Information and Adverse Event Reporting Program Form
ISCO3/LAB/00/04 Physico-chemical characterization of ozonized oil. Peroxide Value
ISCO3/LEG/00/10 Non-recommended routes of application in ozone therapy
ISCO3/QAU/01/03. Madrid Declaration on Ozone Therapy 2020 3th ed. Madrid: ISCO3; ISBN 978-84-606-8312-4; 2020. 104 p.

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10. Documentation and Attachments

Annex I. Informed consent to treatment with O_3

11. Change History

SOP no.	Effective Date	Significant Changes	Previous SOP no.
ISCO3/CLI/00/14	8/05/2023	Draft. Under Revision by Expert Input of Ana Gutiérrez Gossweiler, references were added to the point use of ozonized water in mucositis. Input of Fadi Sabbah, the use of ozonized water in mucositis was rewrite. Minor spelling editing changes. Input of Dr. Adriana Schwartz concerning dose of systemic ways and ozonized oils. Remotion of the recommendation of Coffee enemas. Input of Dr. Gregorio Martínez-Sánchez, the index was reorganized. Text was re-written and supported with additional references. Item 6 was up-dated with the insertion of table 1 by Dr. Gregorio Martínez-Sánchez.	First version
	13/07/2023	The document is archived for the sole confidential use of ISCO3 members, pending further information.	

12. Document Records

	Name	Title	Signature	Date
Author	Wayne McCarthy **E.mail:** doctorozone1@gmail.com	N.D. ISCO3 Member		29/04/2022
Co. Authors / Reviewer / working group	Dr. Suzanne Humphries M.D. and Anna Chirchikova N.D.			
Authoriser / Approved	ISCO3 2020-2024 Approved by majority			07/07/2023

Annex I. Informed consent to treatment with O3

Name surname: _____

Birth place: _____ Date of birth: / /

Address _____

Identity number _____ Phone _____

Medical Facility Address: _____

a) Pathology description: Side effects of cancer therapy. The complementary use ozone pretends to reduce the side effect of chemo or radiotherapy. This treatment proposal is based on the most current knowledge on the subject and is not intended to be a cure.

b) Therapeutic alternatives related to the symptoms presented by the patient: Palliative. Pharmacological treatment of cancer included chemotherapy, immunotherapy or Surgery / Radiotherapy.

c) The medical or surgical treatment that will be performed (explain why and what you want to achieve): __ major auto-hemotherapy __ Rectal therapy ___Ozone infiltration __ Ozonized saline solution __ Ozonized oils ____Ozonized water

d) The therapy before the main treatment: This is a complementary treatment

e) Method of intervention: Sessions of therapy by the way of administration recommended for your physician. A certified medical ozone device is used.

f) Possible treatments or interventions that may be needed in addition to the main treatment: Supportive care, diet, supplements, diagnostic, pharmacological included chemotherapy, radiotherapy

g) Complications: ozone hypersensitivity, vagal syndrome.

h) Side effects that may appear after the treatment: application site pain, application site hematoma.

i) Therapy or indications that must be followed after the main surgery: rest.

The undersigned (taking into consideration the above, with full awareness and freedom) declares

- ✓ Be fully aware,
- ✓ I have carefully read the entire document,
- ✓ That the doctor who will perform the treatment has explained everything necessary for my full understanding of what has been indicated in the document,
- ✓ I understood the content of the document,
- ✓ I authorize the doctor to perform the above medical treatment,
- ✓ That I can leave the treatment when I want,
- ✓ Which can be compensated if unexpected damages appear following the procedure,
- ✓ From now on, authorize the doctor to carry out the procedure described in point f).
- ✓ I understand that I will be given a copy of this consent form.
- ✓ I authorize that my clinical data serve to study the effect of ozone in cancer
- ✓ Authorize the use of me medical records / data, for research purposes.

Date (dd / mm / yyyy) ___/___/ 2023 _____ Patient's signature* _____

*Representative or guardian (in case the patient does not cooperate or is a minor).

Statement from the physician in charge of informing the patient.

The undersigned Dr. _____ confirm and certify, by signing this document, that, in my opinion, the patients understand, point by point, the content of this document.

Date (dd / mm / yyyy) ___/___/ 2023 _____ Doctor's signature * _____

* Everything previously reported in this document offers concise information on the procedure and is not intended to replace the doctor / patient dialogue.