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The use of ozone therapy as adjuvant therapy in cancer: a review of the literature

Final Project Degree in Nursing (2017 – 2018).

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ABSTRACT

Ozone therapy (OT) is a complementary therapy that has been used in the treatment of specific diseases, among which they stand out in recent years in cancer. Therefore, this work is aimed at defining what this therapy consists of, as well as analyzing the effects it has on cancer patients, mainly those undergoing chemotherapeutic or radiotherapeutic treatments. A bibliographic review has been done with exhaustive electronic search in different data bases over a period of 6 months.

Among the various studies found, most agree that medical ozone, due to its properties and mechanism of action, is beneficial in patients with cancer.

Patients with radiotherapy in the area of the head or neck have at risk of osteonecrosis of the jaw, which generates pain, among other discomforts. As a therapeutic measure, medical ozone regenerates the oral tissue and mucosa, which is related to the ability to provide more blood flow to the tissues, which translates into a greater oxygen supply. This is due to the revitalizing and oxygenated capacity of ozone in the face of tumor hypoxia in these pathological processes, together with the damage that occurs in areas where radiotherapy is applied. In the same way, mandibular osteonecrosis can also be produced by chemotherapy drugs in a certain dose.

Keywords: medical ozone, ozonotherapy, cáncer, radiotherapy, immune system, nurse.

1. INTRODUCTION

Cancer is a disease in which the cells of our body begin to divide without control, being able to spread to other tissues, hindering the normal functioning of the body. For this, medicine resorts to different therapeutic alternatives such as surgery, chemotherapy and radiotherapy, being the three best known oncological treatments. However, these procedures cause side effects in the cancer patient, such as osteonecrosis of the jaw (ONJ), hair loss, vomiting, tiredness, weight changes, among others. For this, ozone therapy (OT) can be an effective complementary treatment, which can favor the patient without any risk in the evolution of the disease^[1-3].

Ozone therapy uses medical ozone as a work tool, which is obtained through an ozone generator, where the ozone of the environment is mixed in small doses with oxygen. Note that the reason why ozone therapy does not resort to environmental ozone directly is due to the high toxicity of this^[2-3].

This alternative therapy is used for its mechanism of action on the immune system, since it improves the antioxidant cellular activity by achieving with its application a rebalancing of the cell oxidation-reduction gradient directly, which favors the elimination of free radicals and other reactive oxygen species (ROS), which are found in higher than normal amounts during carcinogenic processes^[2-4].

It should be noted that, under physiological conditions, the formation and elimination of ROS is strictly regulated by endogenous antioxidants and ROS neutralizers with the aim of maintaining homeostasis and avoiding the harmful effects of oxidative stress. However, when the elimination process is not carried out correctly, there is a greater accumulation of ROS, a factor that leads to permanent and harmful changes, such as cell death, carcinogenesis and fibrosis. Faced with this situation, medical ozone is able to activate the nuclear factor 2 related to erythroid 2 (Nrf2), which, in turn, involves the activation of endogenous antioxidants, such as glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD) and glutathione (GSH)^[5-6].

In relation to oxidative stress, the recurrent administration of medical ozone, also known as preconditioning, at non-toxic doses provides an adaptation of the tissues to oxidative stress

by induction of enzymes or activation of the metabolic pathways, maintaining a balanced redox equilibrium as the increase of GSH levels and the decrease of lipid peroxidation^[7].

In addition, oxidative stress is also related to other benefits of OT, this being the oxygenated capacity, which allows the activation of cellular metabolism, which also includes oxidation reactions. This allows to generate the energy that the cell needs, combating the damage produced as a result of deficiency of oxygenation that occurs in carcinogenic processes.

It also provides anti-inflammatory, immunomodulatory and revitalizing effects that, with the other benefits explained, stimulates immunological defenses and promotes the recovery of patients. Therefore, and based on scientific evidence, ozone therapy acts as a complementary therapeutic measure in oncological patients treated with chemotherapy and / or radiotherapy, by reducing the side effects of these treatments, as well as the pathology itself, improving the quality of life, this being one of the objectives of the nursing work^[3-6].

For that reason, among the most relevant complications of radiotherapy in pelvic tumors is prostatitis, although this effect will depend on the patient and the radiotherapy technique. Among the symptomatology that the patients presents is very common rectal bleeding, for which the rectal ozone insufflations, together with the topical application of ozonated oil, are two therapeutic techniques capable of reducing this type of hemorrhage secondary to radiotherapy in the pelvic area, as it happens in prostate cancer^[8-9].

Also, radiotherapy in the area of the head and neck causes numerous side effects in the tissue of the oral cavity, generating ulceration, necrotic mucosa, with exposition of the necrotic bone, accompanied, in some cases, by a slight paresthesia. Because of this, it has been proven through studies that the oxygenation and antioxidant capacity of medical ozone is effective to palliate these side effects of radiotherapy, since it stimulates cell proliferation and soft tissue healing, alleviating the symptoms^[10 - 11].

Like radiotherapy, chemotherapy drugs generate osteonecrosis of the jaw (ONJ), and the use of medical ozone is also appropriate. One of the chemotherapeutic drugs that generate this alteration in the oral mucosa are the bisphosphonates, known in the treatment in conditions related to cancer, such as hypercalcemia and bone metastases associated with breast, prostate or lung myeloma, in combination with anticancer chemotherapy^[12 - 13].

The reason why this drug generates osteonecrosis of the jaw is due to its effects, since bisphosphonates decrease the capacity of the immune response, together with the deterioration of angiogenesis, that is, of osteoclastic function. Thus, ozone activates blood circulation, increases red blood cells, improves the processes of diapedesis and phagocytosis, and stimulates the phagocytic mononucleotide system, thus decreasing symptoms^[13-14].

In addition, at the renal level, chemotherapy drugs for renal susceptibility can generate undesirable effects, such as metotrexate (Mtx) used in many malignancies, but with renal toxicity of 2%. This is due to the precipitation of Mtx that occurs in the renal tubules, together with the decrease in glomerular filtration, causing tissue damage. This situation generates an increase in malondialdehyde (MDA), that is, the existence of lipid peroxidation, which is an important cause of destruction and oxidative damage of cell membranes. For these cases, medical ozone stimulates the activities of antioxidant enzymes such as glutathione, regulating the redox state of the cell. Therefore, ozone therapy is a good therapeutic option, because it has protective and antioxidant effects against nephrotoxicity caused by Mtx^[7].

In the same way, doxorubicin (DOX) is a drug used in a wide range of cancers, which causes several toxic effects, the most common being cardiotoxicity, wearing out the heart muscle and generating dilated heart disease, as well as congestive heart failure, among other cardiac abnormalities that depend on the treatment dose. For this, and according to studies carried out, the preconditioning with medical ozone decreases the levels of pro - BNP, a serum indicator of heart failure, together with the reduction of tenamfetamine, which explains the significant increase in the activities of antioxidant enzymes. This is so, ozone therapy increases survival and decreases the undesired effects of DOX-based chemotherapy treatment^[15].

Another of the consequences in anticancer treatments is pharmacological intoxication, which we can observe in endometrial cancer, whose therapy can be composed of general surgery with hormotherapy, chemotherapy and radiotherapy. This produces toxic and immunosuppressive effects, with an imbalance of the antioxidant system, with medical ozone being a way to reduce pharmacological toxicity, together with modifying the level of

antioxidant protection and normalizing the intensity of lipid peroxidation. It should be noted that, in these cases, ozonated water is advisable due to its antibacterial effects, because it normalizes the values of CD16 + lymphocytes, together with the serum levels of the sCD38, sCD95, sHLA-I and sHLA-DR molecules, whose values increase in tumor processes^[16].

From the nursing perspective, it is important to identify the patient's needs in order to elaborate an adequate plan of care, with the objective of improving the quality of life, trying to reduce and / or alleviate the characteristic symptomatology of the cancer, as well as, in case of treatment, counteract the side effects of it, such as some of those explained above^[1-3].

This work aims to understand the benefits of ozone therapy in cancer patients treated with radiotherapy and / or chemotherapy to improve the quality of life of patients.

Specifically, it is intended:

1. Knowing what medical ozone is.
2. Analysing how radiation therapy and chemotherapy affect oncological patients.
3. Identifying the benefits of ozone therapy in patients exposed to radiation therapy.
4. Describing the benefits of ozone therapy in patients with chemotherapeutic drugs.
5. Comparing the different effects that medical ozone has produced in individuals with cancer to evaluate the recommendation of this unconventional therapy.

2. METHODOLOGY

The methodology chosen for the preparation of this work has been a literature review, carrying out) an electronic search in different data bases offered by the ULPGC, these being PubMed, Cinahl, LILACS, ProQuest, Science Direct, Scielo, Cuiden, Google Scholar, Cochrane , Scopus, and MedLine. For this, the following keywords or descriptors were used: “medical ozone”, “ozone therapy”, “cancer”, “radiotherapy”, “immune system”, with the Boolean connector AND, as shown in (Table 1). However, the results in CUIDEN, Cochrane and Scopus were insufficient for the bibliographic review, because the articles found in these bases did not fit the objectives of this work.

In addition, as inclusion parameters were taken systematic reviews, clinical cases, literature reviews, clinical trials study, cohort studies, descriptive studies, published in English and /

or Spanish from January 2013 to March 2018, free access. As exclusion parameters, any website related to ozone therapy with author absence was discarded, as well as articles that only had a summary.

Table 1: Search strategies by various data bases

Data Bases	Search Strategies
Pub Med	Ozone therapy AND cancer; Medical Ozone AND cancer
Cinahl	Ozone therapy AND cancer
LILACS	Ozone therapy AND cancer
Google scholar	Ozonoterapia AND cáncer
Scielo	Ozone therapy AND immune system
Science Direct	Ti (Ozone therapy) AND Ti(cancer) AND radiotherapy
Proquest	Ab (Medical ozone) AND cancer
Medline	Ozone therapy AND cancer

The electronic search was an advanced search, so the keywords had to be in the subject descriptor, summary, or in the title of the document. In this way, I specified my search to choose the articles that best addressed the topic to be studied from September 2017 to March 2018, reviewing continuously the data bases in case there were new studies on the chosen topic.

3. RESULTS

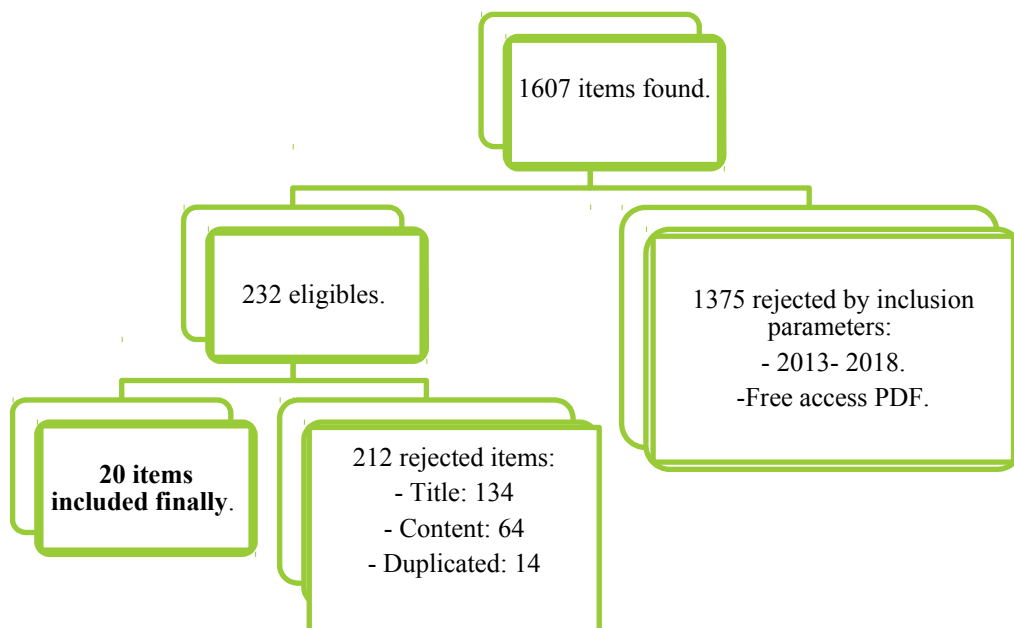
After applying the criteria for inclusion and exclusion, and the different filters used, the following results have been obtained:

Table 2: Search systematics

Data bases	N° ítems found.	N° ítems selected by tracking	N° ítems rejected for being duplicated	N° ítems rejected by contents.	Ítems total
PubMed	331	22	7	3	6
Cinahl	5	2	1	0	1
LILACS	9	4	3	0	1
SCIELO	2	1	0	0	1
GOOGLE SCHOOLAR	599	165	32	4	5
PROQUEST	54	4	2	1	1
MEDLINE	177	24	15	5	1
Science Direct	430	10	4	1	4
TOTAL	1607	232	64	14	20

Finally, 20 articles have been selected, as detailed in Figure 1.

Figure 1: Flowchart: search strategy in databases



In Table 3 the ítems found and selected for the achievement of this work are describes, using the criteria of the Scottish Intercollegiate Guidelines Network (SIGN)¹⁷ for assessing the level of evidence and the degree of recommendation of the selected articles.

Table 3: Summary of the articles included in the analysis of the bibliographic review selected between 2013 and 2018

Authors	Year	Title	Type of study	*LE/ **GR ¹⁷	Sample and features	Procedure developed	Effects obtained	Limitations to consider and observations
Addison CL, Appleton A, Butterfield K, Kuchuk I, Mazzarello S ^[12] .	2013	Oral care and the use of bone-targeted agents in patients with metastatic cancers: A practical guide for dental surgeons and oncologists.	Systematic review.	1+A	A review of the published data in PubMed and meeting abstracts was performed to examine incidence, risk factors, pathogenesis, clinical course and management of osteonecrosis of the jaw with treatment.	Bisphosphonate is an anti-carcinogenic treatment that IV produces oral affectations in patients, which is why antibiotic prophylaxis or the use of alternative therapies such as ozone therapy reduce its incidence, taking into account that there is a percentage to be taken into account. Account that suffers ONJ, of which approximately 30% of patients have pain and exposed bone and an additional 50% suffer pain, gingival inflammation and purulent discharge. In severe cases (around 20%), some patients may progress to a pathological fracture of the jaw, fistula formation, prolonged extended bone necrosis, and a soft tissue infection process.	Ozone therapy (O ₃) in the treatment of bone necrosis or in extraction sites during and after oral surgery in patients treated with bisphosphonate can stimulate cell proliferation and soft tissue healing and relieve symptoms. However, several case reports and small uncontrolled studies reported the controversial efficacy of the O ₃ gas formulation in addition to the conventional one in the treatment of ONJ. In addition, other studies show that medical O ₃ is effective against ONJ if it is administered with antibiotic therapy (azithromycin).	Current data on prevention and treatment of ONJ are relatively poor and are based mainly on case reports, controlled case series, retrospective studies and expert opinions.
Cabezón A, Ceballos D, Clavo B, Fiuza D, Gutierrez D, Lopez L et al ^[8] .	2013	Long – Term Control of Refractory hemorrhagic radiation proctitis with ozone therapy.	Randomized clinical case.	1+B	17 patients with median age 69 years, previously irradiated by prostate cancer that they have persistent or severe hemorrhagic radiation proctitis (HRP) with limited therapeutic options.	Ozonotherapy with ozonized oil and O ₃ gas mixture via rectal insufflations during 15 - 20 minutes. approximately 38 sessions were performed until clinical improvement	This combination of ozone therapy favored beneficial effects in patients, even those who had grade 2 cancer, among other more advanced stages	

*NE = level of evidence. **GR = grade of recommendation.

Authors	Year	Title	Type of studie	*LE/ **GR ¹⁷	Simple and features	Procedure developed	Effects obtained	Limitations to consider and observations
Díaz J, Macías C, Menéndez S ^[5] .	2013	Efecto modulador de la ozonoterapia sobre la actividad del sistema inmune.	Systematic review.	1+A	Bibliographic search with the help of the Teaching General Hospital Roberto Rodríguez Fernández (Cuba), Institute of Hematology and Immunology (Cuba) and Centro Prodanza (Cuba).	Ozone therapy is an interesting technique in the field of application of biological medicine. There are experimental evidences that testify its adequate and safe application in immunological diseases. Therefore, in this article an exhaustive bibliographic search is carried out with the purpose of describing the immunomodulatory properties of ozone therapy, by characterizing the biological effects of ozone on the cells of the immune system.	The medical ozone has beneficiary effects on the immune system, being also an analgesic and anti-inflammatory drug. According to scientific researches, the application of intra-articular ozone, rectal insufflation, among other modes of administration, produces an improvement in patients with immunological alterations, due to the rejuvenating properties, oxygenation, etc; that ozone therapy	
Batinjan G, Filipovic I, Vuletic M, Rupic I ^[10] .	2014	The use in the prevention of osteoradionecrosis of the jaw.	Clinical case.	1+A	A 55-year-old man with metastatic planocellular carcinoma in the area of the right lateral neck. He undergoes radiotherapy for two months in the neck and area of the affected head, which causes candidiasis and severe xerostomia, causing intense pain.	El paciente se somete a cirugía con un post tratamiento de ozono médico. Gracias a esto, las heridas cicatrizaron sin complicaciones, por lo que la ozonoterapia fue una alternativa eficaz.	The authors recommend the substantial need to develop a new protocol for the prevention and treatment of ORN, in which ozone therapy is included as a coadjuvant treatment.	
Bette M, Heinis J, Höffken H, Kinscherf R, Küssner O, Mandic R et al ^[18] .	2014	Intraperitoneal Oxidative Stress in Rabbits with Papillomavirus-Associated Head and Neck Cancer Induces Tumoricidal Immune Response That Is Adoptively Transferable.	Clinical trial.	1+B	40 rabbits in a body weight (BW) range from 2.0 to 3.0 kg. Rabbits were kept in individual steel cages under standardized air conditioning at 20 C to 22 C, 50% to 60% humidity This study has been done according to the German Animal Protection Law.	In the first stage the tumor the animals, which was induced was measured daily. Once they reached a volume above 2500mm ³ , the rabbits were divided into two groups. One group received ozone therapy until the auricular VX2 tumor decreased by 25% of its volume. The other group had simulated treatment receiving anesthesia and peritoneal puncture. The second experimental phase consisted of surgical intervention to analyze the development of possible metastases.	The tumor decreased in the animals that received treatment with O ₃ , while the mice with sham treatment receiving anesthesia and peritoneal puncture, their tumor increased in size. Therefore, the oxidative stress provided by the treatment with intraperitoneal ozone is effective against rabbit VX2 carcinoma associated with papilloma, producing a sustainable oncolytic immune response.	

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Authors	Year	Title	Type of studie	*LE/ **GR ¹⁷	Simple and features	Procedure developed	effects obtained	Limitations to consider and observations
Cañas J, Durán I, Panadés LE ^[11] .	2014	Radionecrosis de Laringe.	Clinical case.	1+A	A 57-year-old male patient with a history of alcoholism and hypertension, who was diagnosed with epidermoid carcinoma of the larynx after dysphonia, dysphagia and aspiration of food.	Radiotherapy is performed to treat larynx carcinoma, a therapy that produces larynx necrosis. To deal with this side effect natural medicine treatment is applied, these being laser or ozone therapy.	Ozone therapy produces a total closure, leaving the patient with natural nutrition. In addition, it should be borne in mind that irradiation of the head and neck can produce a wide range of oral complications.	
Delgado L, González MR, Hernández Y, Martínez G, Medina EA, Morejón, DA ^[15] .	2014	Ozone – oxidative preconditioning prevents doxorubicin – induced cardiotoxicity in sprague dawley rats.	Randomized clinical case.	1+B	Sprague-Dawley rats with a weight between 250 - 300 grams obtained from the national laboratory animal production center of Cuba.	rats were randomly distributed in the following treatment groups: Group 1 were treated with 2 mg/kg intraperitoneal (i.p.) of doxorubicin twice a week for 50 days; Group 2 were treated with 0.3 mg of ozone/oxygen mixture at 50 µg/mL of ozone per 6 mL of oxygen by rectal insufflation and then treated with doxorubicin; Group 3 were treated as Group 2 but only with the oxygen, and Group 4 were treated with oxygen first, and then with sodium chloride i.p. as the control group.	The results showed that ozone therapy preserved left ventricle morphology which was accompanied by a reduction of serum pro-brain natriuretic peptide levels. The cardioprotective effects of ozone-oxidative preconditioning were associated with a significant increase (P <0.05) of antioxidant enzymes activities and a reduction of lipid and protein oxidation.	The results of this study require more pharmacological and toxicological research in humans.
Akyüz C, Aslaner A, Bastürk A, Cakir T, Celik B, Özer A et al ^[7] .	2015	Does intraperitoneal medical ozone preconditioning and treatment ameliorate the methotrexate induced nephrotoxicity in rats?	Clinical trial.	1+B	18 rats with 250 to 300 grams approved by Akdeniz University Local Committee on Animal Research Ethics.	The rats were divided into three equal groups. Group 1 was the control group receiving only physiological saline everyday. Other group receive intraperitoneal Mtx with saline solution. Group 3 was treated with Mtx and medical ozone Within weeks they were sacrificed for histopathological analysis of kidney tissue, and other appropriate tests.	To prevent this nephrotoxicity, the treatment of ozone with a number of pertinent doses generates a protective effect against the characteristic renal lesion in treatments with Mtx. Antioxidant enzymes activated by medical ozone prevented lipid peroxidation and neutrophil infiltration of the renal tissues of Mtx-induced nephrotoxicity in rats. In addition, ozone preconditioning and treatment reduced plasma cytokines and improved histopathological changes of the kidney caused.	It is necessary to do this type of study in humans.

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Aydin T, Akcakaya A, Güneş A, İdin K, Hikmet A, Mayadagli A et al ^[2] .	2015	Medical Ozone and Radiotherapy in a Peritoneal, Ehrlich-Ascites, Tumor-cell Model.	Clinical trial.	1+B	60 male Swiss adult albino mice that were divided into 6 groups, inoculated with Ehrlich ascites carcinoma cells intraperitoneally.	The animals were divided into 6 groups. Some were treated with 2 concentrations of ozone for 10 days. Another group was treated with radiotherapy alone for 5 days. The rest of the groups were treated both with radiotherapy for 5 days and with 10-day ozone therapy of 10 mg / l of concentration, except for one group receiving 20 mg / l. Finally, the control group received 1 ml of 0.9% saline, IP was inoculated for 10 days.	There were differences in weight and abdominal circumference between the different groups, which showed that ozone therapy together with medical radiotherapy increases the survival rate, decreasing symptoms such as ascites and loss of appetite characteristic of this type of cancer.	
Azuma K, Imagwa T, Itoh F, Kawamoto K, Kuroda K, Mori T et al ^[19] .	2015	The Safety and Anti-Tumor Effects of Ozonated Water in Vivo.	Clinical trial.	1+B	BALB female rats with 4-5 weeks old that were prepared to be carriers of colon tumor.	They were divided into 4 groups depending on the route of ozone administration. One was treated intraperitoneally, another was subcutaneously, and the other was IM. The remaining group did not get any type of treatment for colon cancer.	In group 1, who was administered ozone intraperitoneally, no organ abnormalities such as ascites were observed, as was group 3 with ozone IM. On the contrary, the group to which ozone was administered locally (subcutaneously) obtained subcutaneous abnormalities. However, in the group without treatment, the tumor growth rate was higher with respect to the others.	The administration of ozonated water is a safe and potentially simple complement or alternative to existing antineoplastic treatments. However, they assure that it is necessary to continue studying in this field to expand the knowledge.
Bermúdez EB ^[13] .	2015	Análisis de los diferentes protocolos terapéuticos en la osteonecrosis maxilar inducida por bifosfanatos.	Systematic review – meta - analyses.	1+A	Different variables were examined, such as the location of ONJ (jaw, maxilla or both arches), risk factors of ONJ (triggers and contributors), resolution of ONJ lesions and subsequent complications (of ONM lesions or systemic level).	There are different therapeutic alternatives for the management of ONJ such as medical treatment, minimally invasive surgical treatment, surgical treatment and adjuvant measures (ozone therapy). Based on this, 7 protocols are presented, which depend on the efficacy of the stage in which the cancer is found.	Protocol 3 obtains the highest percentage in the healing of ONJ lesions globally, especially in stage 2. (Conservative treatment, clinical and radiological follow-up, minimally invasive surgical treatment and adjuvant measures.) In Stage 0, the one that obtains the highest percentage in the healing of ONM lesions is Protocol 5 (Conservative treatment, clinical and radiological follow-up, invasive surgical treatment and adjuvant measures.).	

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Authors	Year	Title	Type of studie	**LE/ **GR ¹⁷	Simple and features	Procedure developed	Effects obtained	Limitations to consider and observations
Ceballos D, Clavo B, García L, Fiuza D, Gutierrez D, Martínez G et al ^[9] .	2015	Ozone Therapy in the Management of Persistent Radiation-Induced Rectal Bleeding in Prostate Cancer Patients.	Cohort studies.	2+B	Patients previously irradiated for prostate cancer with persistent or severe rectal bleeding in Doctor Negrín Hospital, reviewing previous studies.	Rectal ozone insufflations with concentrations of 5ug / ml and 10 ug / ml, with a subsequent increase to 20 ug / ml and 30ug / ml. They underwent this therapy 3 times a week, until clinical improvement, going to 2 monthly sessions. At the end in 8 of the patients ozonized topical oil was applied to a 25% mixture.	The need for endoscopic processes and blood transfusions decreased markedly after treating patients with rectal bleeding with ozone therapy. Furthermore, rectal insufflations of O ₃ provided a systemic and local effect and the topical application of ozonated oil provided an additional local effect.	The study sample is very limited, in addition to being an uncontrolled study.
Vélez, M ^[20] .	2015	Terapia adyuvante con ozono en paciente con cáncer de páncreas metastásico.	Clinical case.	1+A	Follow-up of a 50-year-old patient diagnosed with pancreatic cancer as a primary tumor with liver metastasis, treated with chemotherapy 40 together with 27 sessions of radiotherapy.	Concomitantly with chemotherapy and radiotherapy, the patient received 157 sessions of ozone therapy. Follow-up is done, studying evolution through controls.	From the hematologic point of view, there were positive variations in platelets leukocytes, hematocrit erythrocytes, etc; returning to more normal values. From the biochemical point of view, glutamyl transferase and alkaline phosphatase were studied, enzymes that are altered in oncological processes. After the sessions, the patient presents a physical and psychological deterioration. However, once the treatment with ozone began, a considerable improvement in their quality of life and psychosomatic symptoms was observed.	Ozone therapy in cancer has not been sufficiently documented, however, with studies such as this, among other types of evidence, affirm the benefits of medical ozone as the improvement in the concentration of triglycerides, or decrease the alteration of chemo and radiotherapy.
Farooqui M, Hassali MA, Shatar AKA, Shafie AA, Farooqui MA, Saleem F et al ^[21] .	2016	Use of complementary and alternative medicines among Malaysian cancer patients: A descriptive study.	Descriptive study.	2+B	393 patients with some type of cancer for at least 6 months and without a conventional treatment duration of more than 5 years.	Two qualitative studies were made in which they explored the behavior of patients towards cancer, the perceptions of the effectiveness of alternative therapies such as ozone therapy and their reasons for using their beliefs.	About 46.1% of patients reported using some form of complementary therapy, especially adult women with breast cancer. However, among the different CAMs, the patients of this study resorted to dietary and vitamin supplements, together with medicinal herbs. Complementary medicine and alternative therapies were divided into categories, with ozone therapy being an energy therapy of medicine according to this study.	It has been a study carried out in Malassia, so it would be necessary to do it in other places and hospitals for more conclusive findings.

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Goncalves FC, Lopez GS, Moraes B, Nascimento RD, Santos LM, Raldi FV ^[14] .	2016	Use of ozone therapy together to low power laser in osteonecrosis induced bisphosphonates	Clinical case.	1+A	Female patient 53 years old with evolution to metastasis of breast cancer treated with intravenous chemotherapy.	Oral lesion secondary to intravenous bisphosphates. He is diagnosed with osteonecrosis in the left maxillary premolar region with small bone exposure. In view of this, ozonated oil is applied at a concentration of 30 mg / ml.	After two weeks of treatment the patient reports a decrease in pain. In addition, after three months with ozonized oil, clinical improvement is observed with bone repair of the jaw.	
Cebeci O, Dillioglul MO, Dillioglul O, Keles ME, Ozkan L, Ozkan T et al ^[3] .	2017	Preventive effect of intravesical ozone supplementation on n – methyl.n-nitrosourea – induced non – muscle invasive bladder cancer in male rats.	Randomized clinical case.	1+A	Male Wistar-Albino rats (n = 51) weighing 200-250 g were used in our experiment at 7-8 weeks of age.	The animals were housed at a temperature of 21 ± 2 ° C with a dark light cycle of 12 h. The rats were randomized into four groups: simulation, instillation with O ₃ only, mnu (induce cancer) alone, or mnu + O ₃ .	Oxidants potentially increase in response to O ₃ , which is counteracted by the simultaneous increase of antioxidants in normal bladder tissue. As such, the mnu + O ₃ group had 28.1% fewer high-grade lesions and bladder carcinogenesis was completely prevented in 16.7% of the rats in this group compared to the mnu alone group. It is noteworthy that no side effects were observed after the application of O ₃ . although it was not statistically significant,	
Franzini M, Giustetto P, Iaffaioli V, Quagliarillo V, Simonetti V ^[4] .	2017	Association of Ozone with 5-Fluorouracil and Cisplatin in Regulation of Human Colon Cancer Cell Viability: In Vitro Anti-Inflammatory Properties of Ozone in Colon Cancer Cells Exposed to Lipopolysaccharides.	Cohort studies.	2+B	To grow human colon cancer cells.	After hours of culture with appropriate growth, different solutions were tested: cisplatin, cisplatin and ozone, 5-FU and 5-FU with ozone. The cells with these solutions were incubated for 24 hours under standard conditions. Subsequently, they were incubated for 4 hours at 37 ° C and a MTT- solution.	This study demonstrates the positive effects of ozone associated with the common anticancer drugs cisplatin and 5-FU, so that this combination increases the cellular cytotoxicity of human colon cancer cells. In addition, ozone is related to Nrf2, which decreases the nuclear factor KAPPA b, being this the most important transcriptional factor involved in various inflammatory processes, as well as the metabolism of cancer.	The limitation these authors find is a critical comparison with the biological effects of ozone on non-cancerous cells.

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Kachalina E, Kontorschikova E, Novikov V, Yanchenko O ^[16] .	2017	The use of Ozonized Physiologic Saline in Gynecologic patients with Uterine Myoma and Endometrial Cancer in the Postsurgical Period.	Clinical case.	1+A	100 women treated at the gynecological clinic of the regional clinical hospital in Nizhny Novgorod with endometrial cancer or stage 1 uterine myoma underwent radical surgery.	They were divided into two groups; one received postoperative therapy, whereas the other group received standard therapy with 10 sessions of intravenous infusion of physiological ozonized saline solution. Analyzes and other tests were carried out with the purpose of studying parameters with antigens CD3, CD4, to study the immunophenotype.	Standard therapy in patients with endometrial cancer and patients with uterine myoma did not receive significant changes in the PBMC repertoire. In patients with endometrial cancer, the relative quantity of CD16 + lymphocytes as well as the serum levels of the sCD38, sCD95, sHLA-I and sHLA-DR molecules fell to normal (p <0.05) only after ozone treatment but not after the standard treatment.	
Morry J, Ngamcherdrakul W, Yantasee W ^[6] .	2017	Oxidative stress in cáncer and fibrosis: Opportunity for therapeutic intervention with antioxidant compounds, enzymes, and nanoparticles.	Systematic review.	1+A	Literature search of different research articles.	Oxidative stress, mainly contributed by reactive oxygen species (ROS), has been implicated in the pathogenesis of several diseases. In this paper, two main examples are reviewed; fibrosis and cancer. Regarding cancer, ROS are responsible for its genomic instability, resistance to apoptosis, proliferation and angiogenesis.	Reactive species are broadly categorized into 4 groups: ROS, reactive nitrogen species (RNS), reactive sulfur species (RSS) and reactive chloride species (RCS), ROS being the most abundant. Furthermore, ROS have a prominent role in the pathogenesis of fibrosis and cancer, due to oxidative stress.	Ozone action to date has suboptimal results.
Buyukpinarbaslili N, Dogan R, Eris AH, Hafiz AM, Kiziltan HS, Ozturan O et al ^[22] .	2018	Effectiveness of radiotherapy + oz one on tumoral tissue and survival in tongue cancer rat model.	Randomized clinical case.	1+A	36 female rats inoculated with cancer.	The rats were divided into 4 groups. One did not receive treatment for induced cancer. Another received as radiotherapy treatment. A third group was treated with radiotherapy together with ozone. Finally, one group received only ozone therapy. At approximately 20 weeks the rats are sacrificed, the tongue is excised, which is stained with hematoxylin and eosin to evaluate hispathological changes.	After studying histopathologically the languages of all the rats, it was demonstrated that radiotherapy plus ozone application provided histopathological improvement and prolonged survival in the advanced rat model with tongue cancer.	

*LE = Level of evidence. **GR = grade of recommendation.

4. DISCUSSION

In relation to the scientific rigor of the design of the studies selected in this work, the hierarchical classification scale of the SIGN evidence has been used for the evaluation of ozone therapy as a complementary therapeutic measure in the field of oncology. The level of evidence found in the literature is mainly composed of articles with a high level of evidence (85%), such as clinical cases and systematic reviews. Likewise, 11 of the 20 articles have a grade of recommendation A. However, the rest of the articles, such as cohort studies, descriptive studies and randomized clinical trials, have moderate evidence (15%). In addition, 45% of the chosen articles have a grade of recommendation B.

In biological medicine is of great interest the use of ozone therapy as a complementary treatment in cancer therapy, however, there are controversies. This type of alternative therapies has increased considerably in recent years among patients with cancer, according to a study conducted in Malaysia, which concluded the improvement in quality of life with the use of complementary treatments, being ozone therapy (OT) a medical alternative^[5, 21].

This beneficial therapeutic effect is due to the properties provided by ozone, being remarkable its oxygenation and antioxidant capacity that counteracts tumor hypoxia and cellular aging of carcinogenic processes. However, ozone has a paradoxical effect, since even having an antioxidant action when its dose is low, it is one of the most oxidizing agents at high doses. For this reason, many studies agree on its proper use provided that the doses are correct^[5].

The main relationship of the OT in the field of oncology, is not the cancer process itself, but the effectiveness of medical ozone in alleviating the effects of radiation therapy and / or chemotherapy according to scientific investigations. One of the consequences of radiotherapy in areas of the head and neck is osteonecrosis of the jaw (ONJ), which, according to various studies, medical ozone would have preventive and therapeutic effects on it. So much so that a study of a patient with metastatic flat cell carcinoma in the neck was subjected to radiotherapy for 8 weeks, which caused candidiasis and oral mucosal lesions due to severe xerostomia. In view of this situation, pre-operative ozone therapy was used as bio-oxygenation therapy, which had positive results on the healing of the oral wounds, which maintains the hypothesis that the properties of medical ozone allow the healing of the mucosa because it induces tissue repair and reduces inflammatory infiltrate. However, there are studies that affirm that in early

stages it is preferable to manage osteonecrosis of the jaw with chlorhexidine - alcohol rinses, together with antibiotic therapy and treatment to remove the pain^[10-14].

To this is added the radionecrosis of the larynx, a sequel that is difficult to demonstrate and, therefore, less known, but to be taken into account according to a study done in Cuba. This is supported by the fact that the oral system is very susceptible to the direct and indirect toxic effects of radiotherapy, being able not only to generate ONJ, but also to affect the larynx system^[11 - 12].

Also, there are chemotherapy drugs that, at certain doses, also generate ONM, such as RANKL and bisphosphonates, especially those administered intravenously. Given this consequence, the administration of ozonized oil for its oxygenating capacity stops the necrotic process of ONJ, such as gingival ulcers with exposed necrotic bone, inflammation and pain, what this is the most frequent complaint in patients. In addition, the combination of medical ozone with laser therapy, according to a study executed, is sufficient to stop this necrotic process, because it promotes the smaller vascular vessels, together with the local biostimulation of connective and bone tissue^[12 - 13].

On the contrary, another study reveals that there are no reports about the direct effects of ozone on tumor cells in vivo, but that in vitro effects have been studied in experimental clinical trials, mainly with rats. In addition, he affirms that ozone gas therapy can become a therapy with toxic results for the respiratory tract of the lung, being dangerous and difficult to manage in Oncology. However, it considers that ozonated water is a safer therapy. In contrast, Clavo and cols propose ozone gas insufflations, together with the topical application of ozonated oil to prevent hemorrhage in prostatitis produced by radiation in pelvic tumors. According to these authors, the application of topical ozone together with rectal insufflations grants the valuable effects of blood flow and oxygenation in hypoxic tissues. In contrast, a higher evaluation in randomized clinical trials, although they argue that ozone therapy may offer a beneficial anti-inflammatory effect similar to that achieved with the use of corticosteroids^[8].

This is supported by other studies, which affirm that rectal bleeding and prostate inflammation are still the most relevant side effects of radiotherapy in patients with prostate cancer (pelvic tumor) on which medical ozone acts. Similarly, another study carried out in the

Oncology Service of Hospital Doctor Negrín affirms that ozonated oil improves the clinical situation, without the appearance of adverse effects. This is so that the OT reduced the number of common blood transfusions before the rectal hemorrhage, because this complementary therapy improves the hemorrheological parameters, as well as inducing a beneficial inflammatory immune response, as reported by other studies. Likewise, chronic ischemia, oxidative stress and inflammation are usually present in the tissues induced in radiation treatment, with ozone being a medical treatment that can modulate these factors, due to its anti-inflammatory effect mainly^[4,9].

Another tissue susceptible to damage of certain chemotherapeutic drugs is the kidney, which is sensitive to methotrexate (Mtx), a cytotoxic chemotherapy drug in the kidneys. In a study, it was concluded that ozone has a protective effect against this type of nephrotoxicity, but for this effect happened, it is necessary to precondition the medical ozone, that is, the repeated application of ozone to increase antioxidant enzymes, protecting the body against cellular damage caused by free radicals, as well as improving the histopathological changes of the kidney caused by Mtx. In addition, this study was based on previous studies conducted in which the levels of inflammatory cytokines, such as tumor necrosis factor, interleukins, which decreased with ozone preconditioning. Specifically, the decrease in MDA levels and the increase in GSH in kidney tissue revealed that preconditioning prevented the kidney from suffering oxidative damage^[7].

In the same way, other studies insure that ozone preconditioning is also an effective measure to prevent the cardiotoxicity induced by doxorubicin (DOX). Because the medical ozone increases the number of antioxidant enzymes and a reduction of oxidized macromolecules, preventing the increase of type B natriuretic peptide precursor of cardiotoxicity. However, this study refers to the need for more research, both pharmacological and toxicological, in order to more accurately determine the clinical efficacy of ozone in pharmacological interventions with DOX in humans^[15].

Another way to apply ozone therapy is in the form of ozonated saline water, which is used in gynecology for patients with uterine myoma and endometrial cancer. Based on scientific evidence, in addition to resorting to ozone therapy to alleviate the side effects of chemotherapy or radiotherapy, it can be used as a post-operative therapy in uterine cancers, with the aim of reducing the risk of intoxication, modifying the level of antioxidant protection

and normalize the intensity of lipid peroxidation and immunity. This fact was experienced by Yanchenko and collaborators who studied the relative amount of CD16 + lymphocytes, among other molecules, which remained at normal levels after ozonotherapeutic treatment, which explains the benefit of this therapy in the immune system in cancer patients. of endometrium and uterine myoma^[16].

Likewise, other studies consider that ozonated water has anti-bacterial effects, being effective, for example, on peritonitis secondary to oncological treatments, as well as being able to inhibit tumor growth through the induction of necrosis of the same. Furthermore, no side effects were observed after this treatment, which supports the proposed theories, with ozonated water being a safe and useful alternative in antitumor treatment, although its most significant results are short-term^[19].

Among the limitations and recommendations of the different authors reviewed, ozone therapy has interesting effects in cancer patients due to its antioxidant, revitalizing and oxygenation properties, among others. Therefore, studies have been conducted to evaluate this effectiveness, with the aim of improving the quality of life of patients undergoing some type of treatment. In general, the scientific evidence coincides with the reduction of aftermath and improvement of symptoms after the application of medical ozone in small doses. However, there are certain limitations in the studies carried out such as the insufficiency of tests, together with the shortage of studies in humans, because experiments have been carried out in animals such as rats and / or rabbits, which, although they confirm the effectiveness of the ozone, it would be advisable to analyze the effects of this therapy in vivo. To this is added that it is important for the nursing discipline knowledge about this novel therapeutic measure, so it would be interesting to continue researching about ozone therapy in order to provide a quality of life satisfactory in patients with some, this being one of the aims of the nursing work. For all this, it would be necessary to launch more exhaustive studies related to the action of medical ozone in cancer patients that provide results of greater evidence and grade of recommendation, with longer duration and with fewer limitations.

5. CONCLUSIONS

Regarding the general objective, most of the scientific evidence found agrees that the application of ozone is an adequate therapeutic measure to reduce the consequence that

treatments are like radiotherapy and chemotherapy, or even in those patients who undergo surgical interventions to remove a tumor.

Regarding the specific objectives:

1. Medical ozone is a medical therapy that has been used in recent years to treat different pathologies, among which is cancer. In oncology, ozone therapy is used because of its mechanism of action that allows clinical improvement in those who undergo radiotherapy or chemotherapy.
2. Radiation therapy affects local tissues, so sessions in the head and neck area have the risk of generating gingival ulcers and inflammation in the buccal mucosa. Similarly, in the pelvic area there is a danger of producing rectal hemorrhage and prostatitis. Likewise, chemotherapeutic agents are pharmacological agents of side effects such as ONJ, hair loss, tiredness and fatigue, which diminish the well-being of users, hindering a positive clinical transformation.
3. The well-known ONM secondary to radiotherapy is produced by the tumor hypoxia that the buccal tissue suffers from this type of treatment in areas of the head. Faced with this situation, the revitalizing, antioxidant capacity, and principally the oxygenation that medical ozone brings to the buccal mucosa, increases blood flow, allowing adequate tissue regeneration. Likewise, in the face of other sequelae such as prostatitis, OT is a therapy that, combined with oncological treatment, allows improving clinical evolution.
4. Bisphosphonates are at risk of generating necrosis in certain tissues. Several studies coincide in resorting to a medical ozone in combination with the chemotherapeutic drug to treat cancer, without producing sequelae, such as ONJ.
5. The treatments that are used to fight cancer are immunodeficiencies, which can produce undesirable effects, which decrease with the application of OT according to the evidence found.

It can be concluded in a general way that, the scientific evidence makes it clear that OT is adequate to complement the secondary treatments of and with, objective, to promote a satisfactory quality of life. However, according to the researchers, the statistics found, human studies are required to protect the response to this type of therapy, hence the importance of investigating the clinical action.

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