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The Utility of Medical Ozone as Integrative Tool in The Treatment of Gastric Cancer

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Abstract

The use of medical ozone in clinical practice showed numerous benefits in the treatment of various diseases, mainly by modulating the immune system and restoring the oxidant/antioxidant balance. Ozone treatment contributes to reducing inflammatory responses and increasing the production of antioxidant enzymes, thus improving the clinical outcome in a wide range of ailments.

Many publications in the last decades showed a positive effect on cancer cells. Furthermore, they confirmed the in vivo and in vitro role of ozone in inducing direct damage to cancer cells, being harmless to non-cancerous cells. In vitro, animal studies and isolated clinical reports suggest the role of medical ozone as an adjunctive treatment in cancer patients by directly potentiating the action of radiotherapy and chemotherapy. In vivo studies have been mainly devoted to the systemic application of low ozone-doses. Randomized controlled clinical trials are in progress with the use of different interventional approaches: specific arterial embolization, intratumoral injection and catheterization. Despite the positive biological effects of ozone, preclinical investigations are needed not only testing more cancer cell lines, but also testing different doses of ozone. Randomized clinical trials are needed to confirm the potential utility of this integrative approach in chemotherapy and radiotherapy.

Key words: medical ozone, ozone treatment, oncology, cancer, oxidative stress, integrative medicine.

Introduction. Although in the last century the incidence of gastric cancer (GC) has steadily and significantly decreased by 2-3% annually, the disease still remains a significant global health burden and one of the leading causes of cancer death worldwide [1]. In Western countries, this fact is partly due to the effective eradication and reduction of Helicobacter Pylori (HP) infection, mainly in cohorts young age, to a better dietary habits and to more frequent cancer screening.

The incidence of GC is projected to trend upward due to an increasing and aging world population, increasing prevalence of risk factors, particularly in people under 50 years of age, and expanding populations in high-incidence developing countries of GC. In this context, a significant increase in the incidence of GC in people aged 25 to 39 years has been reported. According to estimates, in the coming years cancer will take second place as a cause of death [1, 2].

The classic approach of surgical removal followed by radiotherapy and chemotherapy alone or in combination is still valid for many types of cancer, and new treatments such as immunotherapy are showing promising results. Various cellular effects of ozone treatment (OT) have been outlined in recent experimental studies, including resistance to apoptosis of normal cells, inhibition of cancer cell growth, and direct cytotoxic effect with induction of apoptosis in cancer cells. Many of these articles have been published in prestigious journals and describe the ability of ozone to induce direct damage to tumor cells potentiating the effects of radiotherapy and chemotherapy. Nevertheless, nowdays the evidence to confirm a possible beneficial of OT for cancer patients is not sufficiently supported by experimental data reported by the literatures. The few studies that evaluated the effectiveness of OT in cancer patients described the existence of some rational arguments that encourage the use of medical ozone (MO) in cancer. Among these, the improvement of microcirculation and an increased release of oxygen to ischemic and neoplastic tissues, thus ameliorating the general metabolism [3]. Furthermore, MO favours the reduction of oxidative stress through the positive regulation of the antioxidant system, improves the cellular redox potential, induces a mild activation of the immune system, thus ensuring the well-being of patients by activating the neuro-endocrine system [2].

In the context of the above, our review aims to develop a narrative synthesis of contemporary studies to review the current concepts regarding the usefulness of OT in the therapeutic regimen of gastric cancer.

Material and Methods. An initial search of specialized scientific publications was carried out, identified by the Google Search engine and from the databases PubMed, Hinari (Health Internet Work Access to Research Initiative), SpringerLink National Center of Biotechnology Information and Medline. The articles selection criteria included contemporary data on the application and effectiveness of OT in the treatment of GC after the following keywords: "cancer" and "gastric cancer" used in various combinations with the words "ozone", "ozone therapy", "treatment" and "management" to maximize search performance.

For the advanced selection of bibliographic sources, the following filters were applied: articles with full text, articles in English, articles published between 1990-2024. After a preliminary analysis

of the titles, original articles, editorials, narrative synthesis articles, systematics and meta-analysis were selected, which contained relevant information and contemporary concepts regarding the complementary treatment of GC by OT. In addition, a search of the bibliographic reference lists of the identified sources was conducted to highlight additional relevant publications that were not found during the initial database search.

The information from the publications included in the bibliography was collected, classified, evaluated and synthesized, highlighting the main aspects of the contemporary view on the usefulness of OT in the treatment of GC.

In order to minimize the risk of systematic errors (bias) in the study, we performed searches in the databases to identify a maximum number of publications relevant to the purpose of the study evaluating only the studies that met the inclusion criteria.

If necessary, to specify some notions, additional sources of information were consulted. Duplicate publications, articles that did not correspond to the purpose of the work and that were not accessible for full viewing, were excluded from the list of publications generated by the search engine.

Results. After processing the information identified by the Google Search engine and from the databases PubMed, Hinari, SpringerLink, National Center of Biotechnology Information, Medline according to the search criteria, 185 articles were found that address the topic of the application and effectiveness of OT in the treatment of cancer and GC. After the primary analysis of the titles, 35 articles were qualified possibly relevant for the given synthesis. After repeatedly reviewing these sources, 26 publications relevant to the intended purpose were finally selected. In the final bibliography of the work, 26 articles were included, which were considered representative of the materials published on the subject of this synthesis article.

Among the publications selected by the search program, were excluded those that did not reflect the topic of this paper, as well as the articles that were not accessible for free viewing and through the HINARI database or available in the medical scientific library of the Public Institution State University of Medicine and Pharmacy *"Nicolae Testemițanu"*.

Mechanisms of action of MO. OT is performed adminstering a mixture of gaseous ozone with medical oxygen for therapeutic purposes in conditions of chronic hypoxia, inflammation and redox imbalance, as reported in recent literatures [4, 5]. MO is a gaseous mixture of about 95% oxygen and no more than 5% ozone, obtained from medical oxygen by using an ozone generator [4, 5, 6]. OT performed with appropriate dose and exposure time has positive therapeutic effects and must be intended as an adjunct to conventional treatments [5].

The biochemical mechanisms of ozone are well outlined [4, 6]. The clinical effects of OT include:

1. direct disinfectant and trophic (tissue regeneration, healing of wounds and ulcers of various etiologies and refractory with reduction of the associated pain level), when applied locally,
2. systemic antibacterial and antiviral due to a discrete formation of peroxides,
3. antioxidant and cytoprotective by stimulating

the intra- and extracellular antioxidant system with the reduction of oxidative stress damage,

4. anti-inflammatory by suppressing the release of cytokines pro-inflammatory,
5. immunomodulator by activating neutrophils and stimulating the synthesis of some cytokines,
6. relaxation of blood vessels wall throughout nitric oxide (NO) modulation, with the improvement of hemorheological parameters and blood circulation,
7. modulation of erythrocytes metabolism, by increasing the delivery of oxygen to tissues and improving the metabolism of peripheral tissues,
8. analgesic, by neutralizing the action of neurochemical pain mediators, stimulation of the antinociceptive system and the endogenous opioid system [5, 7, 8, 9].

MO multiple effects are mediated by secondary messengers inducing adaptive response from the body. Since the response is mediated by a mechanism involving second messengers, it is not yet clear whether it can be considered according to a dose-effect relationship model.. In addition, ozone indirectly stimulates adaptive mechanisms that can induce modulations in the body by affecting positively the immune system, the blood flow, the realese of oxygen to tissues and the oxidative status of patients. These indirect effects may be potentially beneficial in anticancer therapy [10, 11].

Ozone reacts with interstitial fluids and produces hydrogen peroxide (H_2O_2) in the short term, aldehydes and lipid oxidation products (LOP) in the long term. Acute, moderate oxidative stress induced by low doses of ozone activates nuclear factor erythroid 2 (Nrf2) and modulate positively the antioxidant-prooxidant balance with an increase in the antioxidant system [12, 13].

A small amount of H_2O_2 stimulates nuclear factor kappa B (NF-kB), usually balanced with Nrf2 blocking action, producing immunomodulation with immune system activation by balancing inflammatory/anti-inflammatory cytokines and increasing the amount of oxygen delivered to tissues [3]. Nrf2 activation induces a decrease in NF-kB activity with an anti-inflammatory effect by reducing pro-inflammatory interleukins and increasing anti-inflammatory interleukins. Thus, MO produces beneficial effects by modulating the redox balance, the cellular inflammation status, and inducing an adaptative response. The Nrf2 pathway contributes to confere protection against carcinogenesis, liver toxicity, chronic and inflammatory respiratory diseases, neuronal ischemia and renal diseases [4, 5, 6, 8, 10, 14, 15, 16].

Therapeutic methods and safety of applying MO. As a complementary, adjuvant or palliative cure, OT is increasingly used globally for a wide variety of diseases due to its effects [5]. Ozone has been widely used in many fields, with primary use as a disinfectant. More recently, the use of ozone as an adjuvant therapeutic integration to conventional therapy has also been extended for the treatment of various conditions (dental, musculoskeletal, rheumatic, cardiovascular, neurodegenerative, gynecological, dermatological, infectious, peripheral vascular, etc.), characterized by infectious, hypoxic conditions, chronic inflammation, immune overactivation and oxidative stress. Extensive studies have confirmed the effects and safety of applying MO in various modalities and optimal doses [4, 5, 6, 7, 8, 14, 15,

16].

The ways of administering MO are multiple and vary according to the medical condition, to the pathology to be treated and to the characteristics of the patient:

1. Local or loco-regional: insufflations with oxy-gen-ozone mixture (auricular, vesico-urethral, bags, paravertebral, nasal, oral) [4, 7, 8, 14].
2. Parenteral: systemic (Major Blood Ozonation - MBO, Minor Blood Ozonation – mBO, rectal insufflation (RI) and infiltrative (subcutaneous, intramuscular, intradiscal, intraarticular) [4, 5, 7, 8, 9, 14].
3. Oral and topic administration (ozonated oil, ozonated distilled water, auricolar) [7, 9].

Ozone can be used in different ways provided that it is administered only and always in its native molecular form of O3: ozonated oil, ozonated distilled water, ozone-aerated plastic bags, ozone combined with other substances [14]. For safety reasons, the international society World Federation of Ozone Therapy (WFOT) does not consider ozonated saline solution as a safe method of OT lacking large studies on possible toxicological effects (www.wfoot.org).

The safety dose and clinical protocol are variable depending on the used treatment. In human studies, the safe and non-toxic dose varies between 15 µg/ mL and 50 µg/mL and depends on the type of treatment, the purpose of the treatment and the site of application [14].

A systematic review of the literature has highlighted the safety and efficacy of the systematic application of medical ozone via MBO and RI (17). The authors concluded, that the indications are clearly defined, the applications have become largely standardized and the mechanisms have been well confirmed, the application of low-dose MO is established and proven as a complementary medical method in the treatment of chronic inflammation or diseases associated with inflammatory conditions chronic. More than 11,000 systemic OT in the form of MBO in 577 patients and more than 47,000 RI in 716 patients from different clinical trials were evaluated according to the criteria of evidence-based medicine. Statistically significant improvement in clinical and/or biochemical parameters (antioxidant status or oxidative stress) without side effects or adverse reactions was found in all studies. As a result of the evaluated evidence, the two systemic applications of ozone, MBO and RI, are part of evidence-based medicine, are effective, safe and economical [18].

There are no contraindications for local OT. An absolute contraindication for systemic MO treatment is severe deficiency of glucose-6-phosphate dehydrogenase (favism), an essential enzyme in preventing damage to cellular structures caused by oxidative stress. Relative contraindications for systemic OT are pregnancy, uncontrolled hyperthyroidism, thrombocytopenia, severe cardiovascular diseases, heart failure, convulsive states, hypercoagulability syndrome, individual intolerance to OT components [4, 6].

The incidence of adverse effects of systemic OT is very low and of mild severity (in general, nausea, headache and fatigue, and in the case of RI – transient flatulence and mild irritation), without any influence on the treatment results. Other adverse effects may be determined by incorrect administration technique (vagal crisis, pain,

hematoma at the injection site, local infections) or without a causal relationship between ozone administration and the adverse event [4, 18, 19].

So, the effect of ozone mimics an acute oxidative stress which, if properly balanced, is not harmful, but is capable of causing positive biological responses and reversing chronic oxidative stress [5, 19]. Clinical studies have shown that MBO and RI significantly improves clinical parameters and reference states (antioxidant status, oxidative stress (OS)) without side effects [18].

Potential beneficial effects of MO in cancer treatment. In the last 6-7 decades, publications in reputable journals have shown the positive preclinical effect of MO on cancer cells: they have confirmed in vivo and in vitro the role of ozone in inducing direct damage to cancer cells while being harmless to non-cancerous cells. However, the implementation of these results in clinical practice is far from successful [2, 10, 18, 19].

Because cancer cells have an overloaded antioxidant system due to increased levels of reactive oxygen species (ROS), they have little capacity to increase antioxidant production and, by inducing acute OS, damage the cell. In non-cancerous cells, acute OS as a result of OT produces an activation in Nfr2, which increases the synthesis of antioxidant molecules, and induces a modulation of NF-kβ, which is a crucial mediator of host defense and immune responses. This is why non-cancerous cells can safely handle doses of ozone that are toxic to the cancer cell [2, 10].

The authors of a systematic literature review of a total of 24 in vitro, in vivo and clinical studies provided an overview of ozone as a potential new chemotherapeutic treatment. Starting with an observation in a preclinical study on cells in vitro and in vivo on laboratory animals they demonstrated the possibility of ozone effectively inducing damage to cancer cells while being harmless to non-cancerous cells. The authors concluded that "few clinical articles have been published and therefore there is little evidence-based support for the clinical use of medical ozone in cancer patients". More preclinical investigations are needed to test different cancer cells and different doses of ozone, as different cancer cell lines are not equally affected by ozone. In addition, more in vivo studies are needed to validate the systemic use of ozone as a chemotherapeutic agent [2, 19, 20].

It is well known that tumor hypoxia can cause a 2.5 -3-fold increase in radioresistance and predisposes to a physiological selection of tumor cells with low apoptosis [3]. For several decades, prestigious journals have published in vitro studies on the ability of ozone to induce direct damage to tumor cells and also to enhance the effects of radiotherapy and chemotherapy. Indirect effects have been demonstrated in vivo in animal models: modulation of the immune system, blood flow, oxygenation, oxidative stress, and the sensitizing effect of potentiating radiotherapy and chemotherapy by co-administration of ozone. The effects of ozone in altering the oxyhemoglobin dissociation curve with increased tissue oxygen delivery, 2,3-diphosphoglycerate levels, locoregional blood flow, and tumor hypoxia provide further support for potential beneficial effects during cancer treatment with radiotherapy and chemotherapy [10, 18, 19, 21, 22, 23].

Immunotherapy, the fifth cancer treatment

modality, can be performed either by administering immunomodulatory substances, such as thymus hormones, melatonin, interferons and interleukins, and/or by endogenous activation of the immune system by OS [10, 24]. In addition, MO can improve erythrocyte flexibility and blood rheological properties by decreasing blood viscosity, induce NO production by vascular endothelial cells, and thus produce vasodilation in the microcirculation. As a result, blood flow increases and tumor hypoxia and ischemia are reduced, which is a well-known mechanism for neoplastic cell resistance to drugs and radiotherapy, which enhances neoangiogenesis, dedifferentiation and metastasis [3, 10, 21, 22, 23].

In clinical practice, ozone usually does not come into direct contact with tumor cells, it does not exert a direct effect. Early biological effects are due to the sudden (albeit seconds) increase in ROS (H_2O_2) that initiates a series of biochemical mechanisms in erythrocytes, leukocytes and platelets. Late biological effects are due to LOP with a much longer half-life than ROS [10, 22]. Studies show that ozone can modulate the production of various cytokines (interleukins and interferon) and, as such, modulate the activity of the immune system, which is responsible for the defense of tumor cells [10].

In vivo studies in laboratory animals have demonstrated a significant decrease in the number of metastases, a reduction in tumor development and the rate of increase in tumor volume. The clinical study, carried out on cancer patients, revealed a significant reduction in the side effects of radiotherapy and chemotherapy [22].

Thus, in vitro and in vivo studies in laboratory animals as well as isolated clinical reports suggest the potential role of ozone as an adjuvant during radiotherapy and/or chemotherapy. However, further research, such as randomized clinical trials, is needed to demonstrate the potential utility of medical ozone therapy as an adjunctive therapeutic tool [9, 10, 18, 19, 21, 22].

In cancer survivors with adverse effects of treatments (OS, inflammation, and ischemia), adjunctive OT significantly improves five dimensions of health-related quality of life and significantly reduces toxicity [25].

The possible mechanisms of action of MBO in cancer are [19, 23, 24]:

1. Direct effect of ozone and ROS on cancer cells in vitro and in vivo. Cancer cells live better in a hypoxic environment and have only a rudimentary antioxidant enzyme system to get rid of ROS. Possibly, ozone is able to increase the sensitivity of cancer cells to cytotoxic drugs in vivo. There is a possibility that during ex vivo exposure of the patient's blood to ozone, circulating neoplastic cells undergo severe oxidation and become a potential autovaccine.
2. Improvement oxygenation and metabolism. In cancer, more efficient oxygenation can have a direct inhibitory effect on neoplastic cell proliferation and inhibit neoangiogenesis. In addition, a metabolic enhancement of the immune system may improve immune surveillance, possibly reducing tumor dissemination.
3. Potential regulation of the antioxidant enzyme system with improvement of cellular redox potential. MBO is a procedure that involves a "calculated", transient OS capable of inducing cellular responses with negligible side effects. Ozonated blood, repeated twice a week for at

least a month, stimulates the growth of cellular antioxidant enzymes with the inhibition of OS. This phenomenon of adaptation to OS may be able, at least in part, to explain why ozonated autohemotherapy has a therapeutic activity in ischemic, degenerative, autoimmune diseases and possibly in cancer, where persistent OS has been observed as a factor that favors the progression of invasion and metastasis.

4. Effects on the immune system. It is obvious that due to its strong disinfecting effect, ozone kills bacteria, viruses, fungi, etc., thus facilitating their phagocytosis by leukocytes. Ozone activates both humoral and cell-mediated immune systems (induces cytokine synthesis in monocytes and lymphocytes, triggers a cascade of endocrine secretions).
5. Effects on the central nervous system and the endocrine system. A change in the homeostatic balance evokes a multiorgan response that could positively influence the patient's psychological status, hence the immunological response. There is now some evidence to suggest that OT (with or without other standard treatments) has various therapeutic effects, including in cancer pain management [19].

The results obtained in a study demonstrated the potentialities of MO as an antimetastatic agent and as an adjuvant for the treatment of cancer patients. OT can exert influence at certain points of the complex tumor process. First of all, its effect in regulating oxygen metabolism and oxygenation of tissues has been demonstrated, for example, in the use of the aerobic pathway for energy production and the restoration of normal metabolic functions, controlling lactic acidosis. Then, improving tumor oxygenation through significant and constant availability of oxygen and microcirculation can slow tumor growth and inhibit metastasis. Second, the mild and transient OS produced by this treatment stimulates the growth of cellular antioxidant enzymes capable of inhibiting chronic OS. In cancer, persistent OS has been noted as a contributing factor to the progression of invasion and metastasis. The fact that cancer cells survive better in a hypoxic environment confirms that they have a rudimentary antioxidant system to get rid of ROS. Then, ozone could exert important cytotoxic effects on neoplastic cells if they have a weak defense system. Third, ozone modulates the immune system making it possible to recover the immune response against tumor cells. Human cancer growth has been shown to be inhibited by ozone in culture, suggesting that cancer cells have an impaired defense system against ozone damage [22, 23, 26].

There are several hypotheses that try to explain the mechanism of action of ozonated oils, one of them states that ozone forms hydrogen peroxide and lipoperoxides that would be responsible for the regenerative and disinfecting effects.

In summary, the antimicrobial and restorative mechanisms of ozonated oils are as follows:

- microorganisms are destroyed by direct oxidation;
- compounds formed by ozone are cytotoxic for microorganisms and can inactivate enzymatic key pathways for their survival;
- various components of ozonated oils can release growth factors that can influence tissue remodeling;
- local tissue oxidation by ozonated oil components can stimulate endogenous antioxidant mechanisms and promote tissue repair [27].

Conclusions:

1. The use of MO in clinical practice has numerous benefits in the treatment of various diseases, mainly by modulating the immune system and the oxidant/antioxidant balance, and is applied both locally and systemically. Significant routes of use include intrarectal, subcutaneous, and intravenous. MO treatment contributes in reducing inflammatory responses and increasing the production of antioxidant enzymes, thus improving the treatment of a wide range of diseases. However, MO must be used in the correct concentration range to avoid adverse effects due to high concentration toxicity.
2. The publications of the last decades showed the positive preclinical effect of MO on cancer cells: they confirmed in vivo and in vitro the role of ozone in inducing direct damage to cancer cells, being harmless to non-cancerous cells. In vitro, animal studies and isolated clinical reports suggest the role of MO as an adjunctive treatment in cancer patients by directly potentiating the action of radiotherapy and chemotherapy.
3. In vivo studies have been mainly devoted to the systemic application of low-dose ozone. Randomized controlled clinical trials are the third step, after deeper preclinical studies, with the use of different interventional approaches to ozone distribution in the tumor: specific arterial embolization, intratumoral injection and catheterization.
4. Despite the positive biological effects of ozone, preclinical investigations are needed not only to test several cancer cell lines, but also to test different doses of ozone, since all cancer cell lines are not equally affected by ozone. Randomized clinical trials are needed to confirm the potential utility as an adjunctive therapy in chemotherapy and radiotherapy and the anti-metastatic effect.

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Abbreviations:

The following abbreviations are used in this manuscript:

GC Gastric Cancer
HP Helicobacter Pylori
OT Ozone Treatment
MO Medical Ozone
LOP Lipid Oxidation Products
Nrf2 Nuclear factor erythroid 2
NF-kB Nuclear Factor kappa B MBO Major Blood Ozonation mBO Minor Blood Ozonation
RI Rectal Insufflation
WFOT World Federation of Ozone Therapy
OS Oxidative Stress

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