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High-Dose Ozone Therapy in Oncology Patients: Efficacy, Mechanisms, and Therapeutic Potential

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Abstract

This article provides a systematic review of the effects of high-dose ozone therapy as a complementary treatment in oncology patients. Ozone therapy has shown potential to improve tumor oxygenation, modulate immune responses, and reduce the toxicity associated with conventional cancer treatments. Through systematic analysis of the literature, studies evaluating its efficacy as an adjuvant, its impact on oxidative stress, and its modulation of the tumor microenvironment and patient quality of life are examined in detail. Findings highlight the promise of ozone therapy as an integrative approach that could alleviate the adverse effects of traditional cancer treatments, while also enhancing their efficacy. However, limitations in current studies underline the need for further research to establish optimal protocols and validate long-term benefits.

Keywords

Ozone therapy; Integrative oncology; Tumor microenvironment; Cancer adjuvant therapy

Introduction

Ozone therapy has gained attention in recent years as a promising complementary approach in oncology, primarily due to its unique ability to induce controlled oxidative stress that selectively targets cancer while leaving healthy tissue relatively unaffected. Cancer cells are metabolically distinct from normal cells, exhibiting rapid proliferation, reduced oxidative defenses, and a high reliance on glycolytic

pathways—a phenomenon often described as the Warburg effect [1]. The Warburg effect underscores how cancer cells produce energy predominantly through glycolysis even in the presence of oxygen, a process that results in lower antioxidant capacity and makes them especially vulnerable to oxidative therapies like ozone.

Ozone (O_3) therapy involves administering ozone gas at controlled dosages, leading to the production of reactive oxygen species (ROS) in the body. ROS are highly reactive molecules that can penetrate cellular membranes and cause oxidative damage to vital cellular components such as DNA, proteins, and lipids. This damage, in turn, can trigger apoptosis, or programmed cell death, in cancer cells-a feature that has been widely studied across various cancer types, including breast, lung, cervical, and colorectal cancers [2].

Historically, ozone has been recognized for its antibacterial, antiviral, and anti- inflammatory properties, and it has been used in wound care and as a disinfectant for over a century. Its application in oncology, however, is more recent, with studies exploring its potential to improve tumor oxygenation, support immune function, and alleviate adverse effects of chemotherapy and radiotherapy. Given its unique biologicalactions and minimal toxicity when used correctly, ozone therapy has been proposed as an adjuvant treatment in integrative oncology. This review examines current literature on high-dose ozone therapy, focusing on its biochemical mechanisms, clinical outcomes, and therapeutic potential in cancer care.

Mechanisms of Action

Ozone and reactive oxygen species (ROS)

When ozone is administered, it quickly decomposes to form various ROS, including hydrogen peroxide, superoxide ions, and hydroxyl radicals. These ROS have a profound impact on cancer cells due to their high reactivity with cellular structures. ROS can oxidize cell membrane lipids, disrupt proteins, and cause DNA strand breaks, resulting in cellular damage that cancer cells struggle to repair. The inability of cancer cells to mitigate oxidative damage is attributed to their lower levels of antioxidant enzymes, such as catalase, superoxide dismutase (SOD), and glutathione peroxidase [3].

The presence of ROS in the cellular environment can lead to oxidative stress, a state in which there is an imbalance between ROS production andthe cell's ability to detoxify these reactive intermediates. In cancer cells, which already operate with a reduced ability to manage oxidative stress, the introduction of ozone therapy compounds this stress, overwhelming their defense mechanisms and initiating cell death pathways [2].

Selective toxicity in cancer cells

Cancer cells' selective vulnerability to ozone-induced ROS lies in their diminished antioxidant capacity. Unlike normal cells, which possess a robust antioxidant defense system, cancer cells often lack sufficient levels of enzymes like SOD and catalase, which neutralize ROS. This deficiency makes them more susceptible to the oxidative effects of ozone, while healthy cells can typically withstand low to moderate levels of oxidative stress [1].

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Studies have demonstrated that ozone exposure leads to a concentration- dependent increase in ROS within cancer cells, resulting in oxidative damage that triggers apoptosis. Apoptosis, or programmed cell death, isa controlled process that eliminates damaged cells without causing inflammation—a critical advantage in the tumor microenvironment, where uncontrolled cell death can exacerbate disease progression.

Mitochondrial impact and apoptosis

One of the key mechanisms by which ozone induces cell death is through mitochondrial disruption. The mitochondria are critical for energy production in cells, and their membranes are particularly sensitive to oxidative damage. When ROS levels rise, they can compromise the mitochondrial membrane potential, leading to the release of pro-apoptotic factors like cytochrome c. Once in the cytosol, cytochrome c activates caspaseenzymes, which break down cellular components and ultimately lead to apoptosis [4].

This mitochondrial-targeting effect of ozone is particularly effective against cancer cells, which depend on altered mitochondrial function to sustain their rapid growth. By targeting and disruptingthese energy-producing organelles, ozone therapy impairs cancer cell proliferation while sparing healthy cells that can restore their mitochondrial function more efficiently.

Methodology

A systematic review was conducted using multiple scientific databases, including PubMed, ScienceDirect, and Google Scholar. Search terms included “Ozone Therapy AND Cancer,” “High- dose ozone therapy,” and “Ozone AND Reactive Oxygen Species.” Studies were selected based on their focus on the effects of ozone therapy in oncology, particularly those related to oxidative stress, immune modulation, tumor oxygenation, and quality of life outcomes. The review followed PRISMA(Preferred Reporting Items for Systematic Reviews and Meta- Analyses) guidelines to ensure methodological transparency and rigor [5].

Each study was evaluated for quality and relevance using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method. Studies included a range of research designs, from in vitro and in vivo experiments to observational clinical studies and randomized controlled trials, providing a robust body of evidence on the efficacy and mechanisms of ozone therapy in cancer care.

Results

Effects on oxidative stress and cell death

Ozone-induced apoptosis

High-dose ozone therapy induces apoptosis across a variety of cancer celltypes, including breast, lung, colorectal,and cervical cancers. This apoptotic process is initiated by elevated levels of ROS, which cause oxidative damage to cellular membranes, proteins, and nucleic acids. Studies reveal that ROS production leads to lipid peroxidation and mitochondrial dysfunction, which activate both intrinsic and extrinsic apoptotic pathways. Mitochondrial membrane disruption, in particular, releases cytochromec, triggering the caspase cascade that dismantles the cell [2].

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In studies on breast cancer cell lines, ozone exposure resulted in dose- dependent cell death, with higher concentrations of ozone generating more substantial ROS production and apoptosis. These findings align with similar observations in lung cancer and melanoma cells, where ozone-induced apoptosis has been shown to limit cancer cell proliferation without affecting surrounding healthy tissue [4].

Synergy with chemotherapy

Ozone's synergy with chemotherapy drugs like cisplatin and 5-fluorouracil is a notable benefit, as it enhances drug uptake in cancer cells and amplifies cytotoxic effects. This synergy is especially valuable in patients who experience severe side effects from high doses of chemotherapy. By integrating ozone therapy, clinicians may be able to reduce the dosage of chemotherapy drugs, mitigating adverse effects while maintaining therapeutic efficacy. In clinical studies on cervical cancer, patients receiving combined ozone and radiotherapy exhibited significant reductions in tumor volume and lower gastrointestinal toxicity compared to those receiving radiotherapy alone [6].

In vitro studies on colorectal cancer cells have shown that ozone therapy enhances the effects of chemotherapy by disrupting cancer cell membranes and facilitating drug entry. This disruption weakens cancer cell defenses, allowing chemotherapeutic agents to achieve higher intracellular concentrations and induce greater cytotoxicity [7].

Tumor Microenvironment Modulation and Immunity

Tumor oxygenation

One of the major challenges in on cologyis overcoming hypoxia within the tumor microenvironment, as low oxygen levels contribute to treatment resistance. Ozone therapy has demonstrated a significant capacity to increase oxygenation in hypoxic tumors, thereby enhancing the effectiveness of radiotherapy. In glioblastoma, an aggressive and highly hypoxic tumor type, increased oxygenation from ozonetherapy sensitizes cells to radiation by promoting ROS formation during radiotherapy, which amplifies DNA damage in cancer cells and reduces hypoxia-driven resistance mechanisms [8].

Ozone's ability to improve oxygen diffusion is also valuable in poorly vascularized tumors, which benefit from enhanced blood flow and oxygen supply. By reversing hypoxic conditions, ozone creates a more favorable environment for both chemotherapy and radiotherapy, improving their efficacy against otherwise resistant cancer cells [9].

Immunological Modulation

Ozone therapy has been shown to activate immune responses by increasing ROS production, which stimulates the activity of immune cells like macrophages, dendritic cells, and natural killer (NK) cells. These immune responses are crucial for identifying and destroying tumor cells. ROS from ozone therapy act as signaling molecules that enhance the release of pro-inflammatory cytokines, such as TNF-α and IFN-γ, creating an immune-activated environment conducive to anti-tumor responses [3].

Studies in immunocompromised oncology patients have shown that ozone therapy can reduce markers

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of inflammation and support immune recovery, which is beneficial for patients undergoing treatments that suppress immune function, such as chemotherapy. These immunomodulatory effects suggest that ozone therapy could complement existing cancer immunotherapies, enhancing their efficacy and potentially expanding their applicability [10].

Effects on Quality of Life and Toxicity Reduction

Reduction of side effects

Ozone therapy has been associated with significant improvements in quality of life by reducing common side effects of cancer treatments, including fatigue, nausea, pain, and gastrointestinal issues. These symptoms are often exacerbated by chemotherapy and radiotherapy, which contribute to a decline in patient compliance and well-being. Clinical studies have shown that ozone therapy alleviates these symptoms, allowing patients to better tolerate and adhere to their treatment regimens [5].

Tolerability and safety

The safety profile of ozone therapy is favorable, with minimal adverse effects reported in clinical studies. Ozone selectively targets cancer cells while sparing healthy cells, making it a viable adjuvant to conventional treatments. Patients who receive ozone therapy experience fewer treatment interruptions, faster recovery, and improved physical resilience, which collectively contribute to better outcomes in oncology settings [11].

Discussion

Comparative analysis with conventional adjuvants

Ozone therapy offers unique advantages over traditional adjuvant therapies, such as hyperthermia and high-dose vitamin C, which are also utilized to support cancer treatment. While hyperthermia focuses on raising tumor temperatures to sensitize cancer cells to radiation or chemotherapy, and high-dose vitamin C acts as an antioxidant with potential pro-oxidant effects in cancer cells, ozone therapy provides a dual benefit by both enhancing oxidative stress within tumors and supporting immune modulation. This dual mechanism distinguishes ozone from other adjuvant treatments, as it not only directly targets tumor cells but also promotes an immune response that could further inhibit tumor progression [3].

Comparative studies also indicate that ozone therapy's safety profile is superior to some conventional adjuvants. While therapies like high-dose vitamin C can cause adverse effects such as nephrotoxicity in certain patients, ozone therapy has been shown to be well tolerated with minimal side effects. Moreover, ozone therapy’s ability to improve oxygenation in hypoxic tumors makes it particularly suitable for integration with radiotherapy, which relies on oxygen presence for ROS generation to damage cancer cell DNA [9].

Overall, ozone’s selective cytotoxicity, immune-modulatory properties, and safety profile make it a promising candidate for broader application in integrative oncology. However, limitations in dosing standardization and the absence of large-scale randomized trials have constrained its adoption in clinical settings. Further research comparing ozone therapy head-to-head with established adjuvants is needed to determine its relative efficacy and best- use scenarios.

Mechanistic hypotheses and clinical implications

The mechanistic pathways of ozone therapy are still under exploration, yet current hypotheses suggest that its primary anti-cancer effects arise from a combination of oxidative stress inductionand immune modulation. One prevailing hypothesis is that the ROS generated byozone selectively targets cancer cells due to their compromised antioxidant defenses. Additionally, ozone appears to exert an immunostimulatory effect by activating various immune cells and inducing pro-inflammatory cytokines, which can create an immune-activated tumor environment that further impairs tumor growth and resistance [8].

These effects hold particular significance in cancers known for their immune-evasive properties, such as melanoma and glioblastoma. Ozone's potential to enhance immune responses aligns well with immunotherapy strategies, suggesting that it could be an effective complement to immune checkpoint inhibitors. Some studies suggest that ozone's modulation of the immune microenvironment could potentiate the effects of immunotherapies, making tumors more susceptible to immune attack. However, clinical applications of ozone therapy in conjunction with immunotherapy require further investigation to determine optimal protocols and dosage.

Limitations and areas for future research

Despite promising preclinical and clinical results, the current body of literature on ozone therapy is limited by several factors. First, the lack of standardized dosing protocols makes it challenging to compare results across studies. Different studies employ varying ozone concentrations and administration routes (e.g., intravenous, intraperitoneal, and topical), which can significantly affect outcomes. Establishing consensus on standardized dosages and administration techniques will be essential to advancing ozone therapy in clinical oncology [12].

Additionally, most available studies are small-scale or observational, with limited randomized controlled trials to validate ozone's efficacy and safety rigorously. The heterogeneity of study populations and cancer types also limits the generalizability of findings. Larger, well-designed randomized trials with diverse patient populations are needed to confirm the therapeutic potential of ozone therapy in different cancer types and to explore its long-term effects on survival and recurrence rates.

Finally, exploring ozone therapy in combination with emerging treatments like CAR-T cell therapy, immune checkpoint inhibitors, and targeted therapies could unlock new synergistic effects. Future research should focus onthese combined approaches to assess whether ozone can enhance outcomes when paired with cutting-edge oncology treatments.

Conclusion

High-dose ozone therapy represents a promising complementary approach in oncology, particularly for its potential to reduce the toxicity of conventional therapies, improve tumor oxygenation, and support immune function. This dual action of direct tumor cytotoxicity through oxidative stress and indirect modulation of the immune response makes ozone an appealing candidate in integrative cancer care.

The existing literature indicates that ozone therapy can improve treatment tolerance and patient quality of life, which are crucial factors for maintaining adherence to rigorous cancer treatments. By alleviating chemotherapy and radiotherapy side effects such as fatigue, nausea, and gastrointestinal discomfort, ozone therapy could enhance patient resilience, potentially leading to better outcomes. Furthermore, ozone's ability to improve oxygenation within hypoxic tumors positions it as a valuable adjunct to radiotherapy, as well-oxygenated tumors respond more favorably to radiation.

Despite these encouraging findings, further research is required to overcome current limitations. The lack of standardized dosing protocols and the scarcity of large-scale randomized controlled trials remain significant barriers to widespread clinical adoption. To fully validate ozone therapy as a reliable component of integrative oncology, future studies must focus on developing standardized protocols, conducting multi-center trials, and examining long-term patient outcomes, including survival and recurrence rates.

In conclusion, while preliminary evidence supports ozone therapy as a beneficial addition to conventional cancer treatments, well-designed clinical trials are essential to confirm its safety, efficacy, and applicability across diverse cancer types. Should future research substantiate these initial findings, ozone therapy has the potential to become a valuable tool in comprehensive, patient- centered oncology care, offering improved outcomes and quality of life for patients undergoing cancer treatment.

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