Ozonterapy-Oncology clinical studies

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Original Article

Ozone Therapy for Tumor Oxygenation: a Pilot Study

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Abstract

Tumor hypoxia is an adverse factor for chemotherapy and radiotherapy. Ozone therapy is a non-conventional form of medicine that has been used successfully in the treatment of ischemic disorders. This prospective study was designed to assess the effect of ozone therapy on tumor oxygenation. Eighteen subjects were recruited for the study. Systemic ozone therapy was administered by autohemotransfusion on three alternate days over one week. Tumor oxygenation levels were measured using polarographic needle probes before and after the first and the third ozone therapy session. Overall, no statistically significant change was observed in the tumor oxygenation in the 18 patients. However, a significant decrease was observed in hypoxic values ≤10 and ≤5 mmHg of pO_2. When individually assessed, a significant and inverse non-linear correlation was observed between increase in oxygenation and the initial tumor pO_2 values at each measuring time-point, thus indicating that the more poorly-oxygenated tumors benefited most (rho = –0.725; $P = 0.001$). Additionally, the effect of ozone therapy was found to be lower in patients with higher hemoglobin concentrations (rho = –0.531; $P < 0.034$). Despite being administered over a very short period, ozone therapy improved oxygenation in the most hypoxic tumors. Ozone therapy as adjuvant in chemo-radiotherapy warrants further research.

Keywords: cancer – hypoxia – pO_2 measurement – polarographic probe

Introduction

Tumor hypoxia can cause an increase in radio-resistance by up to 2.5–3 times (1) and predisposes a physiologic selection of tumor cells with decreased apoptosis. This results in additional resistance to radiotherapy and chemotherapy (2) and further increase in angiogenesis and a more aggressive tumor potential (3–5).

Tumor hypoxia, when assessed by polarographic probes, is an independent prognostic factor for response to treatment and/or survival of head and neck tumors (6–9) and uterine cervical tumors (10,11) as well as sarcomas (12,13). The polarographic probe technique was designated as 'gold standard' for tumor pO_2 measurement in a special workshop sponsored by the National Cancer Institute (14), at which the importance of developing methods to overcome tumor hypoxia was emphasized. Since then, meta-analyses have demonstrated that hypoxia modification during radiotherapy can improve treatment outcomes (15).

Ozone therapy has been shown to be beneficial to patients with ischemic disorders, particularly of the lower limbs (16–18). In our previous studies we had found that ozone therapy increases oxygenation in the most poorly-oxygenated tissues of the anterior tibialis muscles (19) and that oxygenation in these muscles might be related to tumor oxygenation (20).

The objective of the present preliminary (and prospective) study is to evaluate the effect of ozone therapy on tumor oxygenation, using the polarographic probe measurement technique.

Subjects and Methods

Patients

Eighteen patients with accessible metastases or advanced tumors were enrolled in the study (14 with head and neck tumors, 2 with gynecological tumors and two bone metastases in chest

wall region). Patients comprised 15 males and 3 females with mean age of 64 years (range, 50–91). The selection criteria included the following: a minimum age of 18 years, Karnofsky performance status of >70%, cancer diagnosis histologically confirmed with metastases or advanced tumors accessible to physical examination and not being suitable for surgical resection. The mean of measured tumors/nodes was 6.5 cm across the greatest diameter (range, 3–12 cm). The exclusion criteria included the following: unwillingness to participate in the study, treatment with experimental or evaluation drugs during the planned study or not fulfilling all of the selection criteria described above. The experimental nature of the study was explained in detail and informed consent was obtained from all patients prior to study. The study was approved by the Institutional Ethical Committee.

Ozone Therapy

Ozone therapy was administered by autohemotransfusion on three alternate days over one week. The procedure involved the extraction of 200 ml venous blood into heparin (25 IU/ml) and $CaCl_2$ (5 mM). Using clinical-grade O_2, the O_3/O_2 gas mixture was prepared with an OZON 2000 device (Zotzmann + Stahl GmbH, Plüderhausen, Germany) and sterilized by passing it through a sterile 0.20-µm filter. The blood was mixed with 200 ml of the O_3/O_2 gas mixture at a concentration of 60 µg/ml, in a single-use sterile container with a capacity of 300 ml. Following this, it was slowly re-introduced into the patient's body. The blood had been extra-corporeal for about 15–30 minutes but no adverse reactions were observed. Table 1 summarizes some of the most relevant clinical characteristics of the patients.

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Table 1. Characteristics of the patients and their tumors

Tumor pO_2 Measurement

Tumor oxygenation was measured using a polarographic probe system: the 'pO_2 Histograph' (Eppendorf AG, Hamburg, Germany). The details of this technique have been described previously (21). Briefly, a 0.5 mm diameter electrode (0.3 mm diameter at the tip) is inserted into the tumor while the patient is under subcutaneous anesthesia. The movement is computer controlled and consists of a 1 mm forward motion and a 0.3 mm backward motion to avoid tissue compression at the measurement site. A pO_2 value is obtained at every 0.7 mm. For each set of measurements obtained, 150–200 single pO_2 values were automatically recorded using at least six different electrode tracks. To determine tumor oxygenation, median pO_2 and the percentage of pO_2 values ≤10 mmHg and ≤5 mmHg were obtained from the pooled data for each individual.

Tumor oxygenation values were obtained on four occasions: First, before session #1; second, after session #1; third, 48 h after session #2 and before session #3; fourth, after session #3.

For each tumor, the change in oxygenation (ΔpO_2) was calculated as the pO_2 value at each time-point relative to the pre-session #1 ('baseline') pO_2 value.

The measurements were carried out on accessible, clinically palpable lymph nodes or subcutaneous metastases without using an imaging technique.

Statistical Analysis

The SPSS 11.0 for Windows software package was used for this study. The distribution of data was assessed by the Kolgomorov–Smirnov test. Two-tailed tests were applied for significance. The paired t-test was used to compare means of all the median tumor values and all the percentages of the ≤10 and ≤5 mmHg measurements. These data are expressed as means ± SD. The Mann–Whitney U test was used to compare the ΔpO_2 between tumors above and below the median baseline pO_2. These data are expressed as median and 25%-75% inter-quartile interval. Linear correlation was assessed by Pearson's r test and non-linear correlation by Spearman's rho test. Differences were considered significant at the $P < 0.05$ level.

Results

- Top
- Abstract
- Introduction
- Subjects and Methods
- Results
- Discussion
- References

Tumor Oxygenation

The patient's individual data for hemoglobin levels and pO_2 values at each measurement time-point are shown in Table 1. Initial tumor oxygenation was 23 ± 5.1 mmHg, and was not related to sex, age, hemoglobin levels, clinical status or tumor size.

After session #1 tumor oxygenation was 31.9 ± 5.1 mmHg, and this difference was significant, $P = 0.009$. However, no statistically significant differences were found in the other two measurement time-point: 48 h after session #2 (27.3 ± 4.3 mmHg) and after session 3 (25.1 ± 3.9 mmHg).

Hypoxic Values

The percentage of values ≤10 mmHg at the baseline proceeded to decrease significantly during ozone therapy from 40.8 ± 7.3% to 27.4 ± 7.3% ($P = 0.002$) after session #1 and to 29 ± 6.2% ($P = 0.039$) 48 h after session #2. The decrease to 31 ± 5.1% after session #3 did not qualify as statistical significance ($P = 0.058$).

The percentage of values ≤5 mmHg at the baseline proceeded to decrease significantly during ozone therapy from 34.8 ± 7.5% to 21.7 ± 6.9% ($P = 0.002$) after session #1, to 23.8 ± 5.9% ($P = 0.045$) 48 h after session 2 and to 23.9 ± 4.9% ($P = 0.033$) after session #3 (Fig. 1).

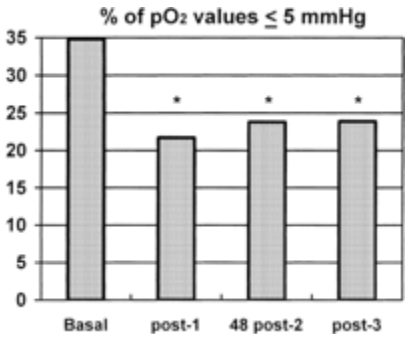

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Figure 1. Change in percentage of pO_2 values ≤5 mmHg. During ozone therapy, a decrease in percentage of pO_2 values ≤5 mmHg at each measurement time-point was observed in the tumors of patients: *Baseline* = before ozone therapy; *post-1* = after session #1 (P = 0.002); *48 post-2* = 48 h after session #2 (P = 0.045); *post-3* = after session #3 (P = 0.033). Significant differences (P < 0.05) are indicated with an asterisk (*)

Factor of Change of pO_2 (ΔpO_2):

At each measurement time-point, an inverse and non-linear correlation was found between individual ΔpO_2 and initial pO_2 values. A higher ΔpO_2 was observed in those tumors that had had lower initial pO_2 values. Significant changes were observed after session #1 (rho = –0.812, P < 0.001), 48 h after session #2 (rho = –0.798, P < 0.001) and after session #3 (rho = –0.725, P = 0.001) (Fig. 2).

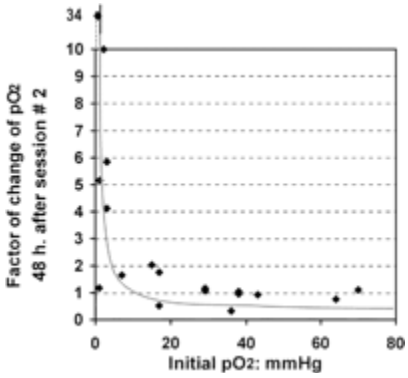

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Figure 2. Factor of change in pO_2 (ΔpO_2) and initial pO_2 For each participant, the ΔpO_2 was calculated as the pO_2 value at each time-point relative to the baseline pO_2 value measured before the start of the ozone therapy. A non-linear correlation was found between baseline pO_2 and ΔpO_2 at each measurement time-point. The figure shows an inverse correlation (rho = –0.798) after session #3 of ozone therapy, which indicates that the highest therapy-associated changes in tumor pO_2 occurred in tumors with the poorest baseline oxygenation. A ΔpO_2 value <1 signifies decrease in oxygenation and ΔpO_2 >1 signifies an increase in tumor oxygenation after session #3.

This was corroborated by the comparison of ΔpO_2 between tumors above and below the median pO_2 prior to ozone therapy (baseline), at each measurement time-point. While the initially well-oxygenated tumors (those above the median) showed oxygenation decrease, the initially most poorly-oxygenated tumors (those below the median) showed an increase in oxygenation after the ozone therapy. The changes recorded were a factor of 2.5 (range, 2–3.1;

P = 0.002) after session #1, a factor of 4.1 (range, 1.7–8; P < 0.001) 48 h after session #2, and a factor of 2.9 (range, 1.1–15; P = 0.002) after session #3 (Fig. 3).

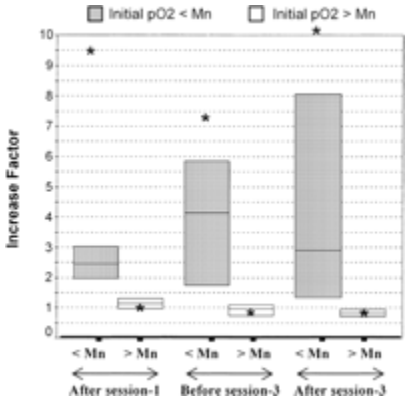

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Figure 3. Factor of change of pO_2 (ΔpO_2) segregated with respect to the initial median pO_2. The figure shows the ΔpO_2 at each measurement time-point following ozone therapy and segregated with respect to baseline pO_2 value above or below the median pO_2 value (17 mmHg) of the overall study group. The boxes show the 25%–75% inter-quartile interval, which includes the 50% values. The horizontal lines in the boxes represent the median and the * represents the mean of ΔpO_2 for both groups of tumors at each measurement time-point. During ozone therapy, well-oxygenated tumors (baseline pO_2 above the median) showed no change (ΔpO_2 approximately 1) or even decrease after session #3 (ΔpO_2 = 0.8). However the most 'poorly-oxygenated' tumors (baseline pO_2 below the median) showed increase in tumor oxygenation (ΔpO_2 >1). These differences were significant at all the three measurement time-points (P = 0.002, 0.001 and 0.002, respectively). < Median = tumors with baseline pO_2 values below the median value; > Median = tumors with baseline pO_2 values above the median value.

Further, at each measurement time-point, an inverse, non-linear correlation between individual ΔpO_2 and hemoglobin levels was found. The ΔpO_2 in tumors was lower in patients with higher hemoglobin levels after session #1 (rho = –0.650, P = 0.012), 48 h after session #2 (rho = –0.531, P = 0.034) and after session #3 (rho = –0.579, P = 0.019) (Fig. 4).

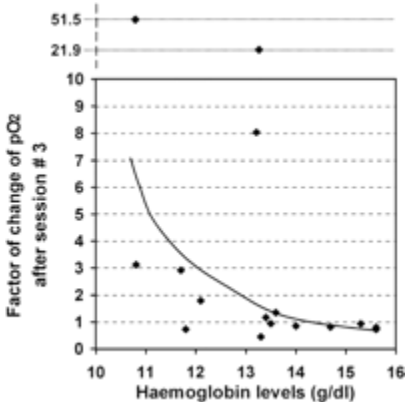

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Figure 4. Factor of change of pO_2 (ΔpO_2) after session #3 and hemoglobin levels. There was an inverse and non-linear correlation between hemoglobin levels and the ΔpO_2 at each measurement time-point following ozone therapy, i.e., a lower effect of ozone therapy was observed in patients with higher hemoglobin levels. The figure shows the correlation with the ΔpO_2 after session #3 (rho = –0.579, P = 0.019).

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Discussion

Ozone (O_3) is the allotropic form of oxygen with three atoms and two unpaired electrons, which has a higher oxidizing capacity than oxygen. In order to avoid lung toxicity, medical applications of ozone require to preclude airways involvement. Autohemotransfusion fulfils this requirement. In appropriate concentrations, this technique leads to a transient oxidative stress that can stimulate blood antioxidants by up-regulation (22–24). This mechanism has been ascribed to ozone therapy's protection against free radical damage of heart (22), and prevention of renal (25) and hepatic (26) disorders. Hemolysis of <2.5% and an acceptable level of lipid peroxide formation has been described in autohemotransfusion at O_3/O_2 concentrations of 60 µg/ml (23).

The objective of the present study was to assess whether changes in tumor oxygenation occurred during ozone therapy. Each patient served as his own control and elective non-ozonated autohemotransfusion was not performed in a separate control group. It was not considered ethical for these advanced cancer patients to undergo invasive study-manipulations over several days in a control group which, theoretically, did not offer any potential benefit (transfusion of oxygenated blood is not a therapeutical approach). On the other hand, several studies have already demonstrated that the administration of ozone-free oxygen in a control group does not produce the 'prooxidant/antioxidant' response necessary to mediate the clinical effects of ozone therapy. This reaction was produced only when ozone was added to oxygen in equimolar amounts (18, 24 and 26).

In the course of ozone therapy by autohemotransfusion, ozone, *per se*, does not enter the organism, and its effects are mediated by rapid (a matter of seconds) oxidation of blood components in the transfusion recipient. The oxidized molecules and the specific antioxidant generated would vary according to the levels of ozone therapy. The vascular effect of ozonated blood transfusion is explained by an increase of malonyldialdehyde and lipid peroxidation leading to leading to activation of the hexose monophosphate shunt with an increased production of 2,3-diphosphoglycerate in erythrocytes (27). This results in a displacement of the oxyhemoglobin dissociation curve to the right and an increase in the release of oxygen to the tissues. A pH decrease in erythrocytes may also shift the oxyhemoglobin dissociation curve to the right (Bohr effect) without modification of 2,3-diphosphoglycerate (28). Furthermore, a charge modification in red cell membranes results in an improvement in membrane flexibility and a decrease in blood viscosity and resistance (18,29). Adenosine, prostaglandins and, especially, nitric oxide release could collaborate in affecting the micro-circulation and lead to a decrease in vascular resistance (30).

Overall, ozone therapy decreased the percentage of values ≤10 and ≤5 mmHg at each measurement time-point. However, no increase was observed in tumor pO_2, as has been reported in an animal study (31). In the present study, the oxygenation decreased in tumors with pO_2 concentrations above the median. Based on the oxygen radio-sensitivity curve, it can be inferred that this is not of clinical relevance in well-oxygenated tumors. However, in tumors with baseline pO_2 below the median, i.e. tumors in which the radio-resistance could increase in relation to this 'adverse' value, ozone therapy actually increased the tumor pO_2. This effect is similar to that observed by us (19) in anterior tibialis muscle tissues following the administration of ozone therapy.

The mechanisms underlying this effect in tumors have yet to be defined. Based on previously described effects, we hypothesize that the inverse correlation between initial oxygenation and ΔpO_2 in tumors and tissues during ozone therapy is secondary to blood flow redistribution, i.e., a drop in blood flow in well-oxygenated tissues in favor of less well-oxygenated tissues. Tumor vessels have structural and functional abnormalities with decreased or absent auto-regulatory mechanisms (32). Hence, an improvement in blood rheologic parameters, as described by other authors (18,29), could play an important role in the effect of ozone therapy in high-resistance systems such as in tumors; this could apply to at least the areas of the tumor that are most hypoxic. Congruent with this concept is the improvement we observed with ozone therapy in patients with lower hemoglobin levels and, as a consequence, with lower blood viscosity. This vascular effect is further supported by our preliminary studies with Doppler techniques, indicating a lasting blood flow increase following three alternating ozone therapy sessions (B. Clavo, personal communication). However, our hypothesis of an increase in tumor perfusion resulting from ozone therapy needs further confirmation with studies specifically addressing the effect on tumor blood flow using, for example, multi-channel laser Doppler.

Techniques such as hyperbaric chambers or carbogen breathing plus nicotinamide can increase arterial pO_2, with secondary tumor pO_2 increase. Usually, however, this is less effective in modifying hypoxic areas and, as well, the effect is of a very short duration; of the order of 10–15 minutes (33). Furthermore, if applied for more than 15–30 min, these therapies can lead to vaso-constriction resulting in a potential blood-flow decrease, secondary to hyperoxia, in most organs (34) as well as in tumors (33). Our results show that, in the most hypoxic tumors, ozone therapy leads to an improvement in tissue pO_2 for at least 48 h after the second session of therapy. Similarly, it should be noted that the hypoxic fraction was decreased for protracted periods. Nevertheless, better results could probably be achieved using combined therapies, principally, techniques to increase blood oxygenation.

On the other hand, metastatic or large-size tumors are probably not the best situations in which to evaluate oxygen delivery or the vascular effect of ozone therapy, as observed in anemia-modification studies (35). However, for the purpose of the present study, the patients selected were those with advanced cancer or with large affected nodes that were easily accessible to physical examination so as to facilitate the tumor pO_2 measurements.

Tumor hypoxia predisposes to a physiologic selection of tumor cells with decreased apoptotic potential, which results in resistance to radiotherapy and chemotherapy (2), higher angiogenesis and a more aggressive tumor potential (3–5). If ozone therapy successfully decreases tumor hypoxia in some patients, it could be useful as an adjuvant in the treatment of these patients by improving tumor oxygenation, by reducing radio-resistance and improving local control. Survival could be improved by decreasing tumor hypoxia, as shown by

Overgaard's meta-analyses (15). The results of the present study indicate that tumor pO_2 modification could support the anecdotal clinical reports of an improved effect of radiotherapy in advanced tumors when ozone therapy is included in the schedule (36).

Radio-mimetic (37) and synergistic (38) effects of radiotherapy as well as growth inhibition of human cancer cells by ozone (39) and increase in chemo-sensitivity in colon carcinoma cells resistant to 5-fluorouracil (40) have been described; albeit, these effects of ozone are not directly applicable to human ozone therapy. However, from a clinical oncology point of view, further research needs to be conducted on the effects of ozone-enriched blood. The effects described in relation to increasing antioxidant (22–26) and cytokine production (41,42) are particularly relevant. A review on the potential role of ozone therapy as a biological response modifier in oncology has been published by Bocci (43), and we concur with the view that the appropriate controlled clinical trials would be particularly valuable.

In conclusion, many aspects regarding the bio-medical application of ozone therapy remain unexplored. In the present prospective study, the effect of ozone therapy on human tumor pO_2 has been measured using the polarographic probe technique, and the results indicate that ozone therapy could increase oxygenation in the most hypoxic tumors. This suggests the potential use of this therapy as adjuvant in chemo-radiotherapy schedules, and would warrant further investigation.

Acknowledgments

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Footnotes

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J Altern Complement Med. 2005 Apr;11(2):257-65.

Restoration of normoxia by ozone therapy may control neoplastic growth: a review and a working hypothesis.

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In contrast to normal tissues, tumors thrive in hypoxic environments. This appears to be because they can metastasize and secrete angiopoietins for enhancing

neoangiogenesis and further tumor spread. Thus, during chronic ischemia, normal tissues tend to die, while neoplasms tend to grow. During the past two decades, it has been shown in arteriopathic patients that ozonated autohemotherapy is therapeutically useful because it increases oxygen delivery in hypoxic tissues, leading to normoxia. Although several oxygenation approaches have been tested, none is able to restore normoxia permanently in patients with cancer. We postulate that a prolonged cycle of ozonated autohemotherapy may correct tumor hypoxia, lead to less aggressive tumor behavior, and represent a valid adjuvant during or after chemo- or radiotherapy. Moreover, it may re-equilibrate the chronic oxidative stress and reduce fatigue.

[tumors radiotherapy under regional hyperoxygenation]
Ambesi, G.; C. Nervi; M. Cortese & C. Casale
Radiologia Medica **55**(3): 193-206, 1969.
ISSN: 0033-8362
PubMed ID: 5202455
Journal written in italian

Summary

After a brief analysis of the physiological and radiological aspects of the irradiation under hyperoxygenation, the authors describe the technique of intraarterial infusion of hydrogen peroxide contemporary to external irradiation they have employed in 65 patients. Data about tolerance and complications ofthe method are discussed. The analysis of results obtained in three groups of patients with different tumors allow the authors conclude that the intra-arterial infusion of hydrogen peroxide is a useful method to increase the oxygenation of a tissue to be irradiated if the equipment for hyperbaric breathing of oxygen is not available.

Cancer. 1965 Oct;18(10):1244-50. Related Articles, Links

Regional oxygenation in the diagnosis and management of intra-abdominal and retroperitoneal neoplasms.

Aronoff BL, Balla GA, Finney JW, Collier RE, Mallams JT.

[Ozone plus cobalt therapy in patients suffering from prostatic cancer]
L. Borrego, L.L. Borrero, E.C. Díaz[1], S. Menéndez[2], L.R. Borrego[3], R.A. Borrego[3].
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Revista CENIC Ciencias Biológicas **29**(3): 137-140, 1998.
ISSN: 0253-5688.
Journal written in Spanish

Abstract

The aim of this study is to evaluate the efficacy of ozone therapy in conjunction with cobalt-60 therapy, in the treatment of patients suffering from prostatic cancer, with regards to a control group without ozone. 70 patients were treated with cobalt therapy, to 35 patients were added rectal ozone. The appearance of side effects (dermatitis radiation, cystitis, proctitis) occurred in 84 % of the patients treated only with cobalt therapy and in 52 % of the patients treated with ozone. Prostatic specific antigen values decreased, less than 10 ng/mL, in 92 % of patients treated with ozone and in 52 % in control group, one month after finishing the treatment. 88 % and 80 %

of clinical and humoral control of the disease were obtained in the ozone group and the control group, respectively, six months later.

Arch Otolaryngol. 1967 Feb;85(2):151-5. Related Articles, Links

Hydrogen peroxide and irradiation of tumors.

Chasin WD, **Gross CC**, **Wang CC**, **Miller D**.

Trans Am Acad Ophthalmol Otolaryngol. 1963 Nov-Dec;67:790-800. Related Articles, Links

INTRA-ARTERIAL HYDROGEN PEROXIDE AND IRRADIATION FOR TUMORS OF THE HEAD AND NECK: A PRELIMINARY REPORT.

Ozon-Sauerstoff-Injektionsbehandlung in der gynäkologischen Strahlentherapie [Intravenous injection therapy with an ozone-oxygen mixture in gynecological radiotherapy]

Hernuss, P.; E. Müller-Tyl & J. Dimopoulos.

Strahlentherapeutische Klinik der Universität Wien, A-1097 Wien, Alserstraße 4, Austria.

Strahlentherapie **148**(3): 242-245, 1974.

Journal written in German

(PubMed)

Abstract

40 female patients with primary and 5 patients with recurrence of genital cancer after treatment have received radiotherapy and a daily parenteral ozone mixture medication. It appears that under influence of the supplementary ozone-oxygen mixture treatment, the regression of female genital tumors in both groups studied was faster. The side-effects of the radiotherapy were reduced and the general condition of the patients improved. The best results were observed in patients with recurrence of poorly oxygen-supplied genital tumors.

Ozon-Sauerstoff-Injektionsbehandlung in der gynäkologischen Strahlentherapie [Intravenous injection therapy with an ozone-oxygen mixture in gynecological radiotherapy]

Hernuss, P.; E. Müller-Tyl & J. Dimopoulos.

Strahlentherapeutische Klinik der Universität Wien, A-1097 Wien, Alserstraße 4, Austria.

Strahlentherapie **148**(3): 242-245, 1974.

Journal written in German

(PubMed)

Abstract

40 female patients with primary and 5 patients with recurrence of genital cancer after treatment have received radiotherapy and a daily parenteral ozone mixture medication. It appears that under influence of the supplementary ozone-oxygen mixture treatment, the regression of female genital tumors in both groups studied was faster. The side-effects of the radiotherapy were reduced and the general condition of the patients improved. The best results were observed in patients with recurrence of poorly oxygen-supplied genital tumors.

Ozon und gynakologische Strahlentherapie [Ozone and gynecologic radiotherapy]

Hernuss P; Muller-Tyl E; Wicke L

Strahlentherapie (1975 Nov), 150(5), 493-9.

ISSN:0039-2073

written in German.

PubMed ID 1216254

Abstract

A short survey is given of the historical development and the physical basis of ozone therapy. Ozone is used in medicine as well as in other spheres. Papers reporting good results of ozone treatment in carcinoma seemed of particular interest. The efficacy of ozone as an adjuvant to the irradiation of carcinosarcomas of rats was confirmed by us. On account of this fact ozone was introduced by us as an adjuvant to the irradiation of women with gynaecological cancer and appeared to give good results. The mechanism of action of ozone is not yet fully clarified and several theories are discussed. Investigations are currently being undertaken in respect to the behaviour of several substances in the organism during ozone therapy.

Cancer outcomes at the Hufeland (complementary/alternative medicine) klinik: a best-case series review.

Jacobson JS, **Grann VR**, **Gnatt MA**, **Hibshoosh H**, **Austin JH**, **Millar WS**, **Neugut AI**.

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PURPOSE: A best-case series review is an efficient tool with which to screen complex complementary and alternative treatments for cancer as candidates for further study. STUDY DESIGN: The National Cancer Institute and other agencies have adopted the best-case series method to evaluate cancer treatments involving complementary and alternative medicine (CAM) for further study. The authors conducted a best-case series review of the Hufeland Klinik. Established in 1985 in Bad Mergentheim, Germany, this facility treats more than 500 cancer patients per year. Hufeland treatment includes dietary modification, injections, ozone therapy, active fever therapy, psychotherapy, and sometimes hormone therapy and/or low-dose chemotherapy. The goal of the treatment is to prolong survival and to maintain good quality of life. METHODS: The clinic provided summaries of 27 cases in which patients with longer than expected survival had agreed to make their medical records available for review. The review involved pathologic confirmation of disease and radiologic confirmation of complete response (CR) or partial response (PR) not attributable to conventional treatment. RESULTS: Based on the summaries and an exhaustive 2-year search for medical records, slides, and imaging data, 12 of 27 cases were selected for full review, and 5 (3 CRs and 2 PRs) were judged best cases. CONCLUSION: Most patients with common cancers receive conventional treatment before coming to Hufeland, and many are treated with chemotherapy and/or hormonal therapy while there. Hence, only a few could be considered for review. With 5 of 12 patients showing a treatment response, the authors conclude that the Hufeland treatment merits further study. They also recommend the development of criteria with which to evaluate best-case series reviews of complex CAM treatments for patients with advanced cancer.

The treatment of malignant diseases with AHIT

Horst Kief
Londoner Ring 105, 6700 Ludwigshafen, Germany.

In: *Ozone in Medicine: Proceedings of the 11th Ozone World Congress* (Stamford, CT., International Ozone Association, Pan American Committee) M-4: 26-31, 1993.
Article written in English

Abstract

The world-wide increase in cancer is a recognized fact. Latest Swedish studies demonstrated an increase in malignancies of up to 40% in the last 10 years in certain industrialized nations. Exact statistical analysis shows that conventional therapy for the treatment of malignant illnesses in the

last 40 years has not resulted in progress except in a minimum of disease processes. New modalities are constantly tested in order to offer optimal results. Regarding the foreground of therapeutic modalities to date, methods can be separated into two groups: 1. With biological and biochemically-treated autologous cancer tissue and 2. Testing with TIL (tumor infiltrating leukocytes) and other immune-competent cells. Due to the direct positive correlation between gamma interferon and interleukin 2 serum levels, and prognosis in the course of malignant diseases, we attempted to cultivate autologous macrophages in our laboratories under low ozone gas conditions in order to stimulate immune competent cells. This laboratory methodology and its resulting clinical efficacy in malignant diseases will be elaborated.

Ozonetherapy in a Complex Treatment of Breast Cancer

Kontorschikova, Claudia N.[1]; Anna V. Alaysova & Igor G. Terentiev.
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Department of Oncology, Nizhni Novgorod State Medical Academy, 10/1 Minin sq., N. Novgorod, 603005, Russia.
In: *Proceedings of the 15th Ozone World Congress, 11th - 15th September 2001, Medical Therapy Conference* (IOA 2001, Ed.), Speedprint Macmedia Ltd, Ealing, London, UK, 2001.

Abstract

There have been followed up 52 women with breast cancer, confirmed histologically, age ranging from 40 to 60 years. 32 patients along with cytostatic therapy have undergone a course of ozone therapy of intravenous infusions or rectal insufflations and ozonated water *per os*. 20 women were on conventional polychemotherapy. The groups were compatible according the age, stage of the disease and accompanying pathology. Involvement of ozone therapy in a complex treatment of patients with breast cancer helped to diminish the incidence and degree of cytostatics toxical side effects, improve their life quality and immunological parameters and significally increase the activity of antioxidant defence system.

: Trans Am Acad Ophthalmol Otolaryngol. 1963 Jul-Aug;67:546-53.

REGIONAL INTRA-ARTERIAL HYDROGEN PEROXIDE INFUSION AND IRRADIATION IN THE TREATMENT OF HEAD AND NECK MALIGNANCIES: A PROGRESS REPORT.

Arch Otolaryngol. 1964 Feb;79:155-9.

REGIONAL OXYGENATION AND IRRADIATION: HEAD AND NECK.

MALLAMS JT, **BALLA GA**, **FINNEY JW**, **ARONOFF BL**.

1: Am J Roentgenol Radium Ther Nucl Med. 1965 Jan;93:160-9.

REGIONAL OXYGENATION AND RADIATION THERAPY: CURRENT STATUS.

MALLAMS JT, BALLA GA, FINNEY JW.
: Fortschr Med. 1979 Mar 15;97(10):451-4.

[Ozone-oxygen therapy for gynecologic carcinomas. The effect of parenteral-ozone oxygen mixture administration on free fatty acids and

triglycerides in patients with gynecologic carcinomas]

[Article in German]

Muller-Tyl E, **Salzer H**, **Reisinger L**, **Washuttl J**, **Wurst F**.

As some authors suspect that ozone influences the metabolic process of fat, we tried to analyse the influence of an ozone-oxygen gas which was applied parenterally. 40 patients with gynecological cancer received 10 ml ozone-oxygen gas with a content of 450 gamma ozone and venous blood was removed before and 10 minutes after application. The serum was lyophilized and the level of fatty acids and triglycerids was determined by the method of Randerath (1965). a statistically significant decrease of the concentrations was observed after application of ozone. Different theories as to the cause of this action are discussed.

Regional Hyperoxygenation: An Important Enhancing Factor of Anticancer Chemotherapy]
Carlo Nervi; Carlo Casale & Massimo Cortese
(Divisione di Radioterapia dell'Instituto Regina Elena per lo Studio e la Cura dei Tumori, Roma)
Tumori **55**: 153-160, 1969
PubMed ID: 4195416
ISSN: 0300-8916
Article Written in Italian

Summary

Tissue hyperoxygenation is an important factor in enhancing the antitumor activity of cytotoxic agents. The authors describe their technique for regional hyperoxygenation by intra-arterial infusion of hydrogen peroxide combined with anticancer agents. The method was tried in 34 patients with extensive head and neck tumors. Objective regression was obtained in 19 (55,7 %). Hyperoxygenation probably influences the cellular metabolic and enzymatic processes, thus enhancing the antineoplastic activity of cytotoxic agents. The method described is useful either as a palliative in extensive inoperable tumors, especially those previously irradiated, or as a first chemotherapeutic step in a comprehensive program of treatment in resistant, slow-growing tumors.

[The therapeutical activity of antiblastic drugs potentiated by means of regional hyperoxygenation]
C. Nervi; C. Casale & M. Cortese
Instituto Regina Elena per lo Studio e la Cura dei Tumori, Roma
Policlinico: Periodico di medicina, chirurgia e igiene Sez. medica **76**(6): 335-342, 1969. [Roma]
PubMed ID: 5396255
ISSN: 0048-4717
Article Written in Italian

Summary

Hyperoxygenation of neoplastic tissues is to be considered as an important factor for potentiating antiblastic activity of chemotherapeutical drugs. The authors of this paper describe the method of regional hyperoxygenation obtained by means of intra-arterial infusion of hydrogen peroxide associated with antimitotic substances. The study we are referring to was carried out in 34 patients suffering from large neoplasms affecting the cervicocephalic region which are thought of as being poorly responsive to therapy. An objective regression of the

disease was obtained in 19 cases (55,7 %). This method is indicated either for palliative treatment of relapsing forms, especially after radiotherapy, or as a first chemotherapeutical step for a radical treatment of slowly growing torpid forms.

Yonago Acta Med. 1967 Oct;11(3):141-9.

Application of hydrogen peroxide infusion to maxillary cancer.

Sasaki H, **Wakutani T**, **Oda S**, **Yamasaki Y**.