# Ozonetherapy in Oncological Clinic

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**Abstract**

The article presents the results received by the authors on having followed 117 oncological patients that were administered medical ozone in addition to conventional combined treatment. Chemiotherapy sessions were found to be less toxic for patients that were on ozonated saline, thus producing less harmful effect on the quality of their life. The emphasis is done on the individual choice of ozone concentration in each case.

## Introduction

At present there are three approaches to the management of oncological patients: surgical intervention, radiotherapy and poly-chemiotherapy [1, 2, 3, 4]. However, it is well known, that blood flowing from the operation wound can contain from 26% to 43% of tumor cell [5]. More over, it is not always possible to perform a radical operation on patients with malignant tumors. Cytostatic therapy and radiotherapy are sure to have various side effects. Neither the development of new cytostatic preparations, nor any improvement in radiation approach seems to result in complete destruction of tumor cells. Some part of these cells still escapes from anti-tumour therapy and stays in an anabiotic condition for a definite period, thus being a potential substrate to cause the relapse of the disease[6]. To provide a long-term control over the tumor process it is necessary to support the compensatory capacities of the organism itself and, especially, those of defense and of regulatory systems. From this point of view, the development of integrative approach to the management of oncological patient seems promising, for it includes in addition to conventional treatment some new methods that can bring to harmony the structure and function of destroyed chains in the immune and neuro-endocrine systems, restoring their interrelations. Ozonetherpay (OT) fits to be one of these methods.

Though ozonetherapy has been used for a long time already and has accumulated experimental evidences of its efficiency in practical oncology, there are still only a few publications on its clinical application. In 1995 A.V. Shakhov and A.B.Terentiev revealed the efficiency of intratumoral administration of ozonated saline for patients with malignant tumors(histologically confirmed), after laryngoectomy with cervical lymphonoduloectomy due to larynx cancer with metastases in regional lymph nodes. They observed restriction of exophytic extention and reduction of tumor volume. It was found expedient to use OT for postoperative patients with lung carcinoma [9] and with urinary bladder cancer [10]. The authors registered significantly fewer cases with purulent complications and fatal outcome. Ozonetherapy in patients with gastric cancer complicated by bleeding helped to normalize pro-antioxidant homeostasis and improve their life quality [11]. According to L.Borrego et al. [12], combination of OT with intra-tellular therapy in patients with prostate cancer enhanced the tumor response to radiation effect and lowered the level of prostate-specific antigen in a shorter period of time, reducing the incidence of radio reactions. Rectal insufflations with ozone-oxygen mixtures in a complex treatment of ovarian carcinomas made it possible to significantly reduce toxic side effects, caused by cytostatics, and to complete the planned therapy. Homeostatic indices in onco-patients were also found improved in post-operation period. Infusions of ozonated saline prior to total hyperthermia in patients with disseminated tumors furthered the abatement of endogen intoxication [15]. V.Bocci [16] used medical ozone to treat reinfused and donor's blood to detoxicate oncological patients receiving impressive results. On having treated blood with ozone. H.Baltin [17] studied the effects of ozone, investigating chemiotaxis and leukocytes phagocytory activity; the changes of the complement system and the circulating immune complexes in oncopatients

The aim of the study was to find out the ways and therapeutic possibilities to use ozonated saline in a complex and combined treatment of patients with malignant tumors, that underwent chemiotherapy in neoadjuvant, adjuvant and follow-up regimes

## Material and methods

There were observed 117 patients with histologically confirmed mammary cancer (MC) of II-IV grade. Ozonated saline (OS) was administered to 48 patients during adjuvant and follow-up courses of polychemiotherapy. The second group was made up of 69 patients (15 patients, in addition to chemiotherapy were on non-ozonated saline). Both groups were comparable according to age group and concomitant pathology. Control group consisted of 30 healthy women of the same age group.

To control patients condition in the course of treatment and to evaluate the effect of the therapy we used: 1)psychological tests (Schpilberger-Hanin tests and Concise version of MMPI), 2) vegetative regulation study( (pulsointervalography), 3)dynamic estimation of antioxidant defense system and lipid peroxidation parameters (tg$\alpha$,$\alpha$, indices of S, Imax, dien conjugates-DC, trien

conjugates-TC,Shiff bases-SB); Of immune status(standard panel of monoclonal antibodies ICO1, ICO 12, ICO 20, ICO 31, ICO 53, ICO 60, ICO 86, ICO 92, ICO 105, ICO 116, ICO 160), of biochemical and general blood analysis. OS doses were chosen individually for each patient. Ozone was generated from “Квазар”(Quazar) medical ozonator(Nizhny Novgorod).

The difference was regarded to be efficiently valid if $p<0,05$. Mathematical calculation of the received data was done by statistic programmes STADIA 4.51 и STATISTICA 5.0. Bonferroni correction was taken into consideration in multiple comparisons

## Results and discussion

The OS use in the first group helped the women to tolerate cytostatic preparations better and improve their general condition. Clinical effect was registered in 84,4%. Intoxication symptoms either disappeared or grew less; cases of nausea and vomiting became less frequent, so were the episodes of headache, cardiac pain and pains in epigastrium and in the colon. . Motion activity as well as work efficiency were increasing. The incidence of infectious complications decreased. OS administration was found to reinforce the effect of cytostatic preparations and induced more rapid regression of auxiliary lymph nodes. Similar OS effect was noted soft tissue metastases. Epithelization of ulcerous skin defects set in earlier in cases when polychemiotherapy was done in combination with OS, than in cases when cytostatic preparations were used without OS.OS infusions in women with metastases of breast cancer, involving the skeletal bones, produced analgesic effect, which enabled them to enlarge the range of motions in shoulder joints and in the lumbar part of the spinal column. There were not noted any cases of side effects or complications due to OS administration. Psychological tests ( Spielberger -Hanin) showed the level off response anxiety to go down after the course of treatment (before – $38,62\pm1,08$ , after – $33,5\pm1,0$, $p<0,05$). The concise MMPI questionnaire revealed the decrease of personality profile level in the scales of neurotic triad, paranoia and psychoastenia. Thus it could be assumed that the patients were getting adapted and the personal stress was abating.

The patients of the second group, on having undergone the course of conventional treatment, complained of weakness, apathy, low efficiency. The treatment was accompanied by increasing episodes of nausea and vomiting, that required additional administration of anti-aemetics**.** Frequent were the cases of clinical manifestations of cardio-, gastro- and hepatotoxicity due to cytostatics. The patients became inert, secluded, complained of general fatigue and lack of interest to the life around. The level of response anxiety did not abate after the course of treatment. The concise MMPI tests showed the elevated level in the majority of personality profile scales according to the baseline parameters and that was indicative of the changes in their psychic activity and adaptation disorders.

The use of non- ozonated saline in the third group did not produce any significant influence on the incidence of unfavorable side effects or changes in psychological test results compared with the patients that received polychemiotherapy only.

The study of vegetative regulation after the course of treatment in patients of the first group revealed the tendency to sympatic tonus elevation and compensatory increase of parasympatic influences. It became evident due to the decline ($p<0,05$) in stress index (SI) and vegetative balance index (VBI). Similar changes indicated the activation of autonomous regulation circuit, optimization of cardiac rhythm, which in its turn reflected the improvement of adaptability of the body systems. However, the influence of the central circuit remained to be the leading one, that was confirmed by valid raise of the centralization index and dynamics in wave structure of cardiac rhythm. LF/HF ratio tended to increase.

In the second group where the women were on chemiopreparations only, the indices of VB, SI, CI and LF/HF ratio were significantly increased ($p<0,05$)., while the indices of variation range were decreased ($p<0,05$) These changes confirmed the increasing stress of regulatory systems and aggravation of the adaptation mechanisms functions. Similar changes in cardiac rhythm variability

were observed in patients of the third group, that were on cytostatics and non-ozonated saline.
Immunogrammes of the patients in the first group that received OS and polychemiotherapy during the adjuvant and follow-up regimes, showed stabilzation of $CD16^+$, $CD22^+$, $HLA\text{-}DR^+$, $CD25^+$ and CD4 cells. Immunoregulatory index above 1,0 was registered in 28 women (58,3%). $CD38^+$, $CD71^+$ cells had a tendency to be increasing. The number of $HLAI^+$ cells was also increased (Table 1).

| Antigen Positive Mono-Nuclear Cells % | GROUPS OF PATIENTS | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 group, n=48 | | 2group=54 | | 3group=15 | | Control Group=30 |
| | Before the treatment | After the treatment | Before the treatment | After the treatment | Before the treatment | After the treatment | |
| CD4+ | 28,24±1,32$^{++}$ | 28,56±,27$^{++}$ | 25,56±1,27$^{++}$ | 26,69±1,22$^{++}$ | 32,20±1,54$^{++}$ | 29,92±1,46$^{++}$ | 41,53±1,89 |
| CD8+ | 24,23±1,67$^{++}$ | 25,81±1,43$^{++}$ | 23,0±0,59$^{++}$ | 29,48±0,24$^{\bullet\square,+,}$ | 27,58±1,27$^{++}$ | 29,78±1,43$^{++}$ | 22,82±1,14 |
| CD16+ | 27,96±1,38$^{++}$ | 26,85±1,29$^{++}$ | 27,85±1,36$^{++}$ | 24,99±1,45 | 25,09±1,0$^{++}$ | 22,50±1,49$^{++}$ | 13,23±0,71 |
| CD25+ | 27,75±1,39$^{++}$ | 27,22±1,36$^{++}$ | 30,07±1,45$^{++}$ | 30,42±1,51$^{++}$ | 30,98±1,49$^{++}$ | 29,17±1,42$^{++}$ | 12,76±2,64$^{++}$ |
| CD38+ | 24,50±1,38 | 27,15±1,26$^{++}$ | 26,40±1,31$^{++}$ | 28,42±1,34$^{++}$ | 27,91±1,35$^{++}$ | 24,93±1,24$^{++}$ | 10,94±0,24 |
| CD50+ | 45,69±2,46$^{++}$ | 50,90±2,49$^{++}$ | 44,39±2,03$^{++}$ | 40,60±2,0$^{\square,1\text{-}2,+}$ | 48,61±2,74$^{++}$ | 46,38±2,27$^{++}$ | 49,76±4,0 |
| CD71+ | 23,65±1,23$^{++}$ | 26,40±1,12$^{++}$ | 27,60±1,24$^{++}$ | 27,35±1,23$^{++}$ | 28,45±1,36$^{++}$ | 28,83±1,38$^{++}$ | 13,06±0,63 |
| CD95+ | 32,55±1,54$^{++}$ | 27,27±1,36$^{\bullet}$ | 27,59±1,48$^{++}$ | 30,60±1,52$^{++}$ | 31,83±1,48$^{++}$ | 29,98±1,46$^{++}$ | 24,14±3,51 |

*Table1 Immunogramme changes in the course of treatment*

*- differences are valid compared with control group: $^+$ - p<0,05, $^{++}$ - p<0,005;*

*- differences are valid compared by the therapeutic methods: $^{\square}$ - p<0,05;*

*- differences are valid within one group$^{\bullet}$ - p<0,05.*

After the course of treatment the number of $CD95^+$ cells lowed down to the normal level. Concentration of IgA had a double increase(p<0,05), identifying the enforcement of secretory defense of mucous membranes. IgM and IgG contents had a tendency to augment. The number of circulating immune complexes (CIC) had a valid reduction.
36 patients (66,7%).of the second group that were on cytostatics had immunoregulatory index below 1,0 after the treatment. There was 10,3%reduction of $CD16^+$ cells, with the decreasing tendency of $CD22^+$ lymphocytes and elevation of HLA-DR levels and augmentation of CD38 cells, $CD71^+$ and $CD25^+$ being stable. The content of $HLAI^+$ cells was found to be enlarged (p<0,05). The content of $CD50^+$ cells was significantly lower than that in the first group (p<0,05). Augmentation of $CD95^+$ cells was observed in 39 patients (72,2%). Average content of $CD95^+$ cells exceeded the norm, that could be because of the fact that both , tumor and normal cells were involved into apoptosis. There was clearly seen the reduction in the concentrations of all classes of immunoglobes- IgA, IgM, IgG and definite elevation of CIC level.
In the third group of patients that were on cytostatic preparations combined with non-ozonated saline, the changes in the immonogram readings were relevant with those of the second group. Before the treatment the index of immunoregulation (IRI) was at the level of 1,13. After the course of treatment it went down to 1,0. Below this level IRI was registered in 9 patients (60,0%). The number of $CD50^+$ cells was lower that in group 1, $CD95^+$ cells being increased in 8 patients(53,3%), the average level of $CD95^+$ cells exceeding the norm. IgA, IgM, IgG concentrations was found to be reduced. CIC level was considerably higher, compared with OS patients.
The received results showed that the use of non-ozonated saline, in spite of its disintoxication effect, did not produce any significant effect on the immune response of the patients compared

with the patients that received ozonated saline. OS immune-correctiion effect seems to be caused by the improved metabolism of immunocompetent cells, resulting in their being more tolerant to cytostatic preparations.
Biochemilumenescent analysis done after the adjuvant or follow-up course of polychemiotherapy combined with OS administration, showed increasing tg$\alpha$ in 27 patients (56,3%), being stable – in 2 women (4,2%). The decreased S ($p<0,05$) и Imax indices that the human organism was able to inhibit the oxidation reactions. The molecular products of lipid peroxidation were diminished: DC -20,4%, TC -60,0% ($p<0,05$), SB -24,9% (Table 2).

| index | Groups of patients | | | | | |
|---|---|---|---|---|---|---|
| | 1 group, n=48 | | 2 group, n=54 | | 3 group, n=15 | |
| | Before treatment | After the treatment | Before treatment | After the treatment | Before treatment | After the treatment |
| tg$\alpha$, | 0,58±0,09 | 0,70±0,06 | 0,51±0,16 | 0,41±0,08□,1-2 | 0,64±0,13 | 0,45±0,06□,1-3 |
| S | 26,48±2,24 | 18,93±1,05• | 24,22±2,71 | 27,18±2,84□,1- | 27,73±2,38 | 23,83±2,63□,1- |
| Imax | 3,40±0,64 | 2,90±0,56 | 2,77±0,48 | 3,56±0,52 | 3,60±0,35 | 3,06±0,29 |
| DC | 0,49±0,12 | 0,39±0,09 | 0,42±0,11 | 0,37±0,09 | 0,47±0,14 | 0,44±0,11 |
| TC | 0,40±0,12 | 0,16±0,03• | 0,36±0,06 | 0,36±0,10□,1-2 | 0,39±0,11 | 0,35±0,09□,1-3 |
| SB | 10,16±1,74 | 7,63±1,82 | 9,57±1,38 | 10,72±1,87 | 11,05±1,89 | 8,71±1,63 |

*Table 2. Changes in lipid peroxidation in the course of treatment*

*- differences are valid compared by the therapeutic methods: □ - p<0,05;*

*- differences are valid within one group• - p<0,05.*

The decreased content of final LP products provided the reduction of Intoxication symptoms in this group of patients. The observed OS effect was similar to the results received by several authors[18]. It proved the possibility of compensatory mobilization of endogen antioxidants and activation of antioxidant defense system.
Other biochemical indices were returning to the normal level as well. By the end of the treatment aspartataminotransferase activity had 22,1% reduction($p<0,05$), apaninaminotransferase - 24,3% ($p<0,05$), $\gamma$-glutamintransferase -52,6% ($p<0,05$), total bilirubin- 15,6%, ($p<0,05$ ). Thus, it became evident that the liver structure and function were also going through normalizing processes and it allowed to support//maintain haemostatsis of the patients

The use of ozonated salined helped to maintain the level of hemoglobin and of leukocytes in peripheral blood that made it possible to complete the prescribed treatment in all the patients without any breaks. No cases of deep thrombocytopenia were noted.
In patients that were on polychemiotherapy only , the tg$\alpha$ value was lower than those in OS patients ($p<0,05$) and compared with the initial level in 28 women(50,0%).
However, the differences in tg$\alpha$ values before and after he treatment were not proficient , that might be explain by the effect of glucorticoid preparation, known to capturie free radicals, that were included into PCT schemes and not by increased resources of endogene antioxidants. That assumption was confirmed by the increase of S and Imax indices (17,2% and 30,9%) after the course of treatment, S index being significantly different from that in the 1st group.

The end of the treatment was marked by DC reduction with TC either remaining stable or being higher than in OS patients, SB had an increasing tendency. The use of non-ozonated saline combined with polychemiotherapy showed the decreasing tendencies in the values of tg$\alpha$,S index and LP molecular products and stabilization of Imax.

Biochemical blood analysis of the second group patients revealed activation of liver enzymes: transaminases and $\gamma$-glutamiltransferase ($p<0,05$), the increase of the total bilirubin level indicating

the increasing damage to liver function. The haemogram displayed the increase in anaemia, leukopenia, thrombocytopenia. Intravenous infusions of non-ozonated saline as a method of detoxicating therapy, did not improve the results of the treatment.
The received findings testified to OS efficiency in oncological patients, which could be explained by the following facts. Ozone is known to be of high biochemical selectivity concerning double-bond compounds: aromatic amino acids, peptides, poly-nonsaturated fatty acids [19,20], OS therapeutic effects can be achieved as a result of ozonides formation [21], direct metabolic action [22], and intoduction of a small amount of free radical products [23] Free radicals of the oxygen alike molecular phagus, can recombinate with endogene free radicals, thus activating antioxidant defense system and enhanced cellular metabolism. Ozonides penetrating haematoencephalitic barrier or working on segmental level can act as “triggers” launching neurophysiologic reactions revealing themselves as metabolic mediators for intracellular, systemic and intersystemic integration and produce multifactor influence on pathogenesis, course and outcome of the disease [24]. Specific ozone-induces shifts peforming the role of sanogenesis in oncological pathology can be the following: pro-antioxidant regulation, elimination of tissue energetic deficiency [18,31,32,35], immunomodulating effect [14,26,30], detoxication effect [15,32,37], remodeling(correction) effect on the condition of the nervous system [23,24,38-41 ] anti-tumor effect [25,42-48].

We should bear in mind that OS effect depends on the dosage. To correct the haemostasis and provide optimal course for adaptation processes low ozone concentrations were advisable[ 48].

## Conclusion

The presented results provide convincing evidence for ozonetherapy to be included into combined management of patients with malignant tumors. It helps to reduce the incidence of side effects due to chemiotherapy and to improve the therapeutic effect, making the quality of patients life better. Individual ozone doses and careful control of lipid peroxidation changes helps to prevent the development of oxidative stress. All these factors make ozonetherapy a safe method to be used in clinical practice for in- and out-patient clinics

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