Ozonetherapy in a Complex Treatment of Breast Cancer

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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 to the age, stage of the disease and accompanying pathology. Involvement of ozonetherapy 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 significantly increase the activity of antioxidant defense system.

Introduction

The recent years have been marked by a growing incidence of breast cancer (BC) in many of economically developed countries. BC has become the most common oncological pathology in women since the beginning of 1980-s and in Russia it has moved to the first place (17.4%) among malignant tumors and to the second place (13.7%) concerning the mortality rate (4). In Russia BC is daily diagnosed in 102 women, 50% being malignancy of III-IV stage (3).

Cancer is considered to be a free radicals pathology. In 1998 N.Emanuel (17) having referred to typical regulations of tumor development, suggested the hypothesis of free radicals (FR) playing an important role not only in the primary mechanisms of cancerogenesis but in the further tumor development An important role of free radicals oxidation in pathogenesis of malignant development was later confirmed by different authors both in Russia and abroad (9,10,14,15,20). The quantity of free radicals and LP products changes according to the stage of oncological development. It cannot be excluded that severe toxical events that occur at the terminal stage of the disease are caused by accumulation of hydroxidative radicals in the organism (16,18).
The essence of the mechanisms of chemotherapy and radiotherapy that are widely used in the BC treatment can be reduced to free radicals release. Their excessive accumulation has a damaging effect on membranes both of tumor and healthy cells, causing serious metabolic disbalance, resulting in functional disorders of different organs. In these conditions special attention should be attached to coordinated interaction between pro-oxidant and antioxidant systems, being a significant indicator of physiological resistance of the organism to these factors (6,19). However, endogenic system of antioxidant defense (AOS) cannot cope with the intensification of oxidative processes. AOS activity in oncopatients was found to be

significantly reduced compared to that of healthy people (2,11,12,). The decline of AOS compensatory capacity can be caused by inhibition of synthesis and increased consumption of its components and also by hydro- and lipoperoxides hindering their activity**,** as well as by complicated use of endogenic antioxidants due to microcirculation disorders and membrane resistance.

It is the disbalance between AOS and LP activity that leads to the development of severe toxicosis in patients receiving conventional treatment, aggravates their life quality and often makes it necessary to discontinue the treatment, thus affecting its efficacy (1).

The conception of FR important role in the development of tumor process opened new ways in the search for new anticancerogenic and antitumor medications as well as for correction of toxical side effects of chemo- and radiotherapy. Involvement of different antioxidants into a complex and combined treatment of oncopatients seems to be much promising. Of all available antioxidants preferable choice should be given to medical ozone. Ozone has systemic effect on hypoxia correction, improvement of metabolic processes, it activates the immune response and capacity to detoxification, results in better blood rheology and microcirculation, corrects AOS condition (5,7,8,13,21).

At present ozonetherapy has been successfully used in therapeutic practice as well as in surgery, obstetrics, gynecology and pediatrics. Of special importance is the development of schemes and recommendations to use medical ozone in the treatment of oncopatients.

The aim of the present study is to estimate the efficacy of ozonetherapy in the complex treatment of patients with breast cancer.

Material and Methods

We have followed up 52 patients with breast cancer in the age of 40-65 years with histologically confirmed diagnosis. All patients have undergone conventional treatment that included mastectomy, radiotherapy, cyclic courses of polychemotherapy. Along with cytostatic therapy 32 patients were on ozonetherapy of intravenous infusions of ozonated saline, rectal insufflations and ozonated water *per os,* 20 patients were entirely on conventional polychemotherapy. The groups were compatible according to the age, stage of the disease and accompanying pathology. According to International classification TNM, 60% of the both groups had III and IV stages of tumor process. The most common accompanying pathologies were the diseases of gastro-intestinal tract (chronic gastritis and chronic cholecystitis) and of cardio-vascular system (hypertension).

Laboratory control over the treatment included the assessment of hemogram and immunogram readings, biochemical blood analysis. The intensity of LP processes was measured by dien and trien conjugates levels (DC and TC) and by Shiff bases (SB). DC and TC contents were estimated by ultraviolet spectrum of lipid solution absorption in methanol-hexan, the wavelength being 233nm and 275 nm respectively. SB contents were defined with fluorimetric method (DL Fletcher, 1973) with excitation wavelength of 365 nm and emission wavelength of 420nm. AOS activity was calculated by the index of chemolumenescence lightsum (S) in plasma, the sloping rate of FR oxidation process in plasma (tgά), I max reflecting potential capacity to LP and Imax/S coefficient. All results

were received by the method of induced chemolumenescence done with the use of БХЛ-06 device (Russia).

Immune status was assessed by reactions of indirect immunofluorescence with monoclonal antibodies to superficial antibodies of CD $^{4+,}$.CD^{8+} CD $^{38+,}$ CD^{22+},CD $^{95+}$.In addition concentrations of immunoglobulins IgA,IgM,IgG were estimated. All analyses were done before and after the course of Ozonetherapy and after the cycles of polychemotherapy.

To produce medical ozone there was used medical ozonator «Квазар» adjusted to the system of pure oxygen distribution. Ozone was used in a form of ozonated saline for intravenous infusions (0.9%NaCl solution).

Results and Discussion

The estimation of LP and AOS condition in 50 patients with breast cancer showed the changes of this value to depend on the stage of the disease. The lowest SB level was registered in patients with stage I (Table I) .At stage III it reached its maximal value. In women with disseminated process SB index was similar to that of the stage II.

Table I. The Condition of Lipid Peroxidation and Antioxidant System Activity in Patients with Breast Cancer According to the Stage of the Disease

Index	BC Stage			
	I (n=10)	II (n=10)	III (n=15)	IV (n=15)
SB	2,96±0,12	6,31±0,29	7,19±0,32	6,45±0,31
Imax	1,0234±0,03	2,395±0,115	2,027±0,093	1,908±0,042
S	10,55±0,42	16,96±0,74	13,58±0,61	14,66±0,68
Imax/S	0,102±0,001	0,140±0,005	0,126±0,005	0,124±0,004
tgα	0,486±0,018	1,883±0,081	1,983±0,089	0,547±0,023

There were insignificant changes in DC and TC indices. The value of Imax, S, I/S were minimal at stage I, raised to their maximal level at stage II and then gradually lowered down with the development of the process.
Dynamics in tgα level corresponded to the changes in SB contents raising to its maximal value at stage III and coming down to the level of stage I in patients with dissemination.

Thus, if at the initial stage of breast cancer we could observe LP/AOS balance, with the course of the disease LP processes started to predominate while AOS was losing its compensatory capacities. Administration of cyclic courses of polychemotherapy led to gradual deficiency of AOS components and made it necessary to add antioxidantive agent to the schemes of chemotherapy.

Estimation of immune condition of the patients was done with the use of monoclonal antibodies. During the courses of cytostatic therapy we could observe the decrease of T-lymphocytes level due to CD $^{4+}$cells. The reduction of CD^{8+}cells was less pronounced. The quantity of CD $^{95+}$cells gradually increased. It can be explained by the involvement of cells damaged by cytostatics into apoptosis. At the same time there could be observed inhibition of humoral immunity that was manifested in the decrease of CD^{22+}cells and of concentrations of immunoglobulins of all types. Similar changes in immune parameters occurred irrespective of the stage of the disease. Gradually patients were found to develop

ischemic signs of immune-deficiency. During the period between the courses of polychemotherapy the patients were subjected to acute bacterial or viral diseases and exacerbation of chronic diseases (chronic cholecystitis, chronic pyelonephritis, chronic bronchitis). The manifestation of immunedeficiency clinical signs urged to use additional medications with immunomodelling action.

Cyclic courses of polychemotherapy were accompanied with gradual growth of toxical side effects of cytostatics. Due to cumulative effect of antrocycline antibiotics there developed elevation of cardiotoxicity. During the course of treatment there was a proportional raise in the incidence of gastro-intestinal disorders, hepatotoxicity. The patients often developed episodes of conditioned-reflectory vomiting to a possible taking of new medications. Hemogram readings showed increasing events of anemia and leucopenia.

Thus, the results of the preliminary examinations stipulated the choice of an agent capable to produce antioxidant, desotoxical and immunocorrecting effect. At the same time the agent was not to increase the cytostatic toxicity and not to have dyspeptic or hematological side effects. In our opinion, medical ozone met all these requirements.

The use of ozonetherapy made it possible to significantly reduce systemic non-specific activity of cytostatic agents in 24 patients (75%) and to diminish side effects of polychemotherapy in other cases, however it did not eliminate them completely Ozonetherapy made it easier for the patients to survive the courses of polychemotherapy. They had fewer episodes of nausea and vomiting, diarrhea, of pains in the epigastrium and in large intestine, of cardiac rhythm disorders and less infectious complications. All of them noted better appetite, sleep, general wellbeing, ability to work and to move. Some patients stated less edema and numbness of the arm on the damaged side and increased volume of joints movements. Evidently, in this case the effect of ozonetherapy was connected with improvement of microcirculation.

Analysis of LP products showed decrease in SB contents (45.4%), DC(32.8%) and TC (48.1%) with simultaneous AOS activation (Table II). Biochemolumenecsent analysis of blood plasma revealed 21% decrease of S value with 66.3% increase of tgα and no changes of J max.

Table II. Dynamics in LP and AOS Parameters in Patients with Breast Cancer in the Course of Cytostatic and Ozone Therapy

Index	Group I (n=32)		Group II (n=20)	
	Before	After	Before	After
DC	0,58±0,02	0,39±0,02	0,54±0,02	0,50±0,02
TC	0,27±0,02	0,14±0,01	0,23±0,01	0,20±0,01
SB	5,38±0,21	2,94±0,09	5,04±0,21	5,58±0,23
S	13,79±0,54	10,89±0,42	15,10±0,69	19,24±0,72
Imax	1,506±0,04	1,479±0,05	2,009±0,09	4,453±0,18
Tgα	0,34±0,01	1,01±0,04	0,33±0,009	0,16±0,005

Note: Group 1- patients on Cytostatic and Ozone Therapy
Group 2 – patients on Cytostatic Therapy

Estimation of immune status proved ozonetherapy to produce an activated effect on immune system with a tendency of CD $^{4+}$cells and of immunoregulatory index to increase. The contents of CD $^{38+}$ cells had 15.1% raise with CD^{22+} and CD^{95+} coming to normal range.

IgM had a double increase (0.68 ±0.05 g/l before and 1.43 ±0.3g/l after the treatment) . Concentrations of IgA and IgG tended to increase.

Biochemical blood analysis evinced decrease in the levels of glucose and of urea, total, direct and indirect bilirubin (Table III**).** Improvement of oxidative-reduction processes was confirmed by normalization of alanin-and aspartat-transaminases activity(Al - As -At).

Table III. Changes in Biochemical Parameters in Patients with Breast Cancer in the Course of Cytostaic and Ozone Therapy

Index	Group I (n=32)		Group II (n=20)	
	Before	After	Before	After
Glucose	5,3±0,22	4,0±0,15	5,0±0,18	6,3±0,29
Urea	5,8±0,14	4,3±0,18	6,1±0,26	7,8±0,28
AlAt	29,0±1,36	20,0±0,93	30,0±1,24	56,0±1,3
AsAt	32,0±1,25	19,0±0,74	31,0±1,38	45,0±2,14
Total bilirubin	16,0±,05	11,0±0,42	15,0±0,5	18,0±0,4
Direct bilirubin	4,0±0,1	3,0±0,12	3,0±0,09	3,0±0,11
Indirect bilirubir	12,0±,03	8,0±0,1	12,0±0,3	15,0±0,63

Note: Group 1- patients on Cytostatic and Ozone Therapy
Group 2 – patients on Cytostatic Therapy

Hemogram readings showed increase in leukocytes due to ozone effect that resembled the effect of corticosteroids. The development of deep thrombocytopenia and pronounced disorders in coagulogram were not registered in spite of the use of cytostatic medication and ozone hypocoagulative effect. Throbocytes level did not extend the normal range. There were no cases requiring to discontinue the course of polychemotherapy or ozonetherapy and to administer hemocorrecting medication.

The preliminary findings received in the course of experiments testify ozone capacity to potentiate the action of cytostatic agents

The patients of the control group during the course of cytostatic therapy exhibited increasing fatigue syndrome. they complained on weakness, apathy, insomnia, less capacity to work, regular episodes of nausea and vomiting. The women noted increased feeling of anxiety and irritability. If after the first course of polychemotherapy some patients along with LP activation had compensatory elevation of AOS activity, with the course of treatment they displayed the exhaustion of AOS potentials. The course of polychemotherapy resulted in the following data: S value had 20.6% increase, tgα -51.5% decrease, Imax had double increase (Table II).

Immunogram demonstrated gradual lessening of CD^{4+} and CD^{38+} cells. The contents of CD^{38+} cells had no evident changes while. CD^{95+} cells tended to increase. Concentrations of immunoglobulins diminished to the lower limit of the normal range.

Biochemical analysis of blood revealed gradual elevation of the levels of glucose, urea alanin-and aspartat-activity and increase in total, direct and indirect bilirubin (Table III). Hemogram showed the events of leuko-and lymphopenia, anemia. In some cases the course

of treatment had to be discontinued and additional medications of desotoxicative and hemocorrective agents to be administered.

Conclusion

The received results give profound evidence of ozonetherapy efficacy in the complex treatment of breast cancer. The use of ozonetherapy made it possible to significantly decrease the incidence of systemic non-specific side effects of chemo-prepararions and improve the quality of life of oncopatients in the course of treatment. Medical ozone makes it possible to elevate AOS activity and normalize LP processes. Ozone immunomodelling effect is revealed in the correction of immune status indices, thus eliminating the use of medicinal immunomodulators and reducing the number of infectious complications. Normalization of leukogram parameters ensures complete course of cyclic cytostatic therapy (no interrupted courses or forced reduction of doses).

Improvement of oxidative-reduction processes and of microcirculation yields to reduce hepato- and cardiotoxicity of cytostatics and to eliminate or diminish the dosage of accompanying therapy, to normalize biochemical blood analyses.

Individual selection of single doses of ozone and thorough control over LP changes helps to prevent the development of oxidative stress and makes the method safe and easy to use in the clinical practice.

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