TISSUE HYPOXIA IN TUMOR-BEARING ORGANISM AND ITS POSSIBLE ROLE IN CANCER THERAPY

Summary. On the basis of the results of own and literature data reasons for the development of tissue hypoxia in the organisms with a malignant tumor are validated, as well as the assumption that tissues hypoxia of the tumor-bearing organism is its natural adaptive response. The occurrence of malignant tumors leads to a substantial change in the relationship of the organism with the environment, so the search for effective means of treatment for malignant disease must be tailored to the triad: «tumor — organism — environment». Favorable results can be achieved, provided that the adaptive reactions of the patient are able to normalize its relations with the environment. The possibility of the use of homeopathic and alternative therapies in oncology is considered. It has been argued that adaptation of the patient can be achieved through a homeopathic remedies applied on a background of reduction of adaptation tension of organism (for example, located in external hypoxic conditions) or change certain parameters of the environment.

Hypoxia of intact tissues of organism at tumor process is established fact [1–3]. It is considered that tissue hypoxia is a sign of suppressive impact of malignant tumors; it is aggravated in terminal stage of disease and decreases at successful treatment [2, 4]. Thus, there is direct correlation between level of hypoxia and progression of malignant process. At tumor process changes manifest itself not only on physiological and biochemical level (decrease respiration intensity and oxidative phosphorylation, increase of glycolysis level, alteration of microenvironment and pH medium), but also on genomic and epigenomic level [5]. Decrease of content of oxygen in normal tissues contributes to the emergence of embryonic features of cells as well as increase of content of carbon dioxide, which stimulates the expression of mitotic genes; due to decrease of concentration of oxygen, the water-structural homeostasis that, in turn, causes the malignant transformation of genetic apparatus of cells. Detected features of changes of oxygen metabolism in tissues at tumor disease contributed to the fact that significant efforts of oncologists were aimed at elimination of tissue hypoxia with the help of hyperbaric oxygenation and antihypoxants [6–8]. At the same time, there is another way to overcome tissues hypoxia at the expense of natural hyperbaric (stay of organism under the conditions of highlands) or artificial hypoxia [9, 10].

According to the concept of carcinogenesis [11], presence of malignant neoplasm causes the direct suppression of functioning of antioxidant systems and overoxidation of both tumor and normal tissues. Overoxidation contributes the rapid growth of tumor; stay of organism under hypoxic conditions is accompanied with decrease of intracellular pO₂ and peroxide oxidation of lipids of tissues, activation of antioxidant systems of different level. Thus, in organism of bearer of tumor normalizes bioenergetics and cellular metabolism. Finally, it may cause the inhibition of its growth. Data of available studies [9] are the evidence that stay of organism under hypoxic conditions increases the capacity of respiration system, transport of oxygen by blood, microcirculation in tissues, amount of erythrocytes in blood, increases affinity between hemoglobin and oxygen. Upon such conditions, the compensatory mechanisms of organism adaptation to hypoxia engage, which cause the generation of hyperoxic conditions of functioning of cells after their adaptation to hypoxia. At such adaptation the super-recovery of oxygen metabolism in tissues takes place. In authors opinion, such influence looks like homeopathic principle of therapy – «similiasimilibuscurantur» («likes are cured by likes»). The same view have other researchers [10], in whose opinion, stay of organism upon hypoxic conditions causes the successive engaging of cellular, subcellular and molecular mechanisms of adaptation that results in occurrence of compensatory physiological shifts, which allow to overcome harmful impact of tissue hypoxia conditioned by different diseases. In such situation normal atmosphere pressure for organism turns out to be “increased”.

It should be noted that mentioned data [9, 10] are not enough informative for adequate understanding of cause of occurrence of tissue hypoxia of organism at tumor process and favorable action of external hypoxic conditions. In our opinion, tissues hypoxia at tumor process is the result of not only suppressor impact of tumor, but also natural adaptive responses of organism to the “increased” content of oxygen in environment, i.e. in atmosphere. Primary cause of such response is decrease of general metabolism, oxidative phosphorylating as well as disorder of antioxidant systems [11, 12].

Such state causes earlier acceptable normal oxygen pressure of environment becomes redundant, since it does not correspond with new antioxidant capabilities of organism at tumor disease and in order to survive it has to accommodate itself to the environment again with the help of adaptation mechanisms.
Certainly, adaptive responses of organism are permanently changing cause of inconsistency between demands of organisms and parameters of environment. This inconsistency may occur both at change of parameters of environment (at unchanged state of organism) and at change of state of organism (at unchanged features of environment) [13, 14]. Changing homeostasis, tumor process causes the alteration of microcirculation of blood and lymph, suppresses breathing and oxidative phosphorylating, decreases activity of antioxidant systems in healthy tissues, i.e. creates “cancer background” that causes as the final result death of ill organism [2, 3].

Thus, hypoxic state of tissues at tumor process is adaptive response, which contributes to the survival or increase of life expectancy of patients with malignant neoplasms. Therefore placement of patients upon conditions of hypoxia is not “like cures like” and not adaptation training [9, 10], but its switch to more adequate (by oxygen content) conditions, staying in which approximates organism of patient to the state of “physiological rest” [15], reduction of reactions, which are accompanied with loss of energy, worsening of living condition of malignant cells. Our position does not coincide with notions of some domestic and foreign researchers.

If we do consider, according to the data of mentioned researches, that positive influence of hypoxic conditions lies in adaptation training, which increases the physiological capabilities of organism, then it should be noted that there is ambiguity of understanding of essence of adaptation in respect to the changing environment.

It is known that transfer of organism both in less and more comfortable physiological conditions is accompanied with its adaptive responses. At analysis of states, which in first case are characterized by more, and in second case – by less compensatory tension of adaptive responses, it should be recognized that mechanisms and energetic price for these adaptive processes may be different. For this reason, by analogy with stress classification [16], first variant of adaptation may be designated as dysadaptation. Accordingly, for example, processes of oxygen metabolizm, which take place at transfer of organism from normoxic to hypoxic conditions, should be determined as favorable, to hyperoxic – as dysadaptation. It may be supposed that upon different conditions clinical course of tumor process and treatment with use of one or another methods and means or without them may be different.

Correctness of our notions concerning the reasons of hypoxia of tissues at tumor process is supported by the following facts. According to the data of series of authors [9, 17], increased concentration of oxygen in respiratory atmosphere (up to 96–98 vol.% in 5.0–21.6% of cases is intolerable for patients with different diseases, including patients with malignant tumors. At the same time, hypoxic gas environment (nitrogen — 90%, oxygen — 10%) did not withstand only 1.0% of patients. Hyperoxigenation (96–98 vol.%) in patients with decreased tolerance causes the paradox response – decrease of oxygen pressure in tissues, alteration of breathing in cells of different organs. Long staying of organism even of almost healthy people upon hypoxic conditions of spaceships accompanied with decrease of consumption of oxygen, development of anemia, activation of lipid peroxidation [18].

Results of carried out studies allow to conclude that capacity of human cellular antioxidant systems is close to maximal (utmost) value as applied to atmosphere environment containing 20.9% of oxygen. Paradox reaction and intolerance of oxygen is response of patient organism to unacceptable concentrations of oxygen in atmosphere and, probably, it shows indirectly that conditions with lower content of oxygen in inspired air are more preferable for it.

The transfer of patients and healthy people from normoxic to moderate hypoxic conditions of highlands essentially increases their adaptive mechanisms that, in turn, cause the essential increase of unspecific resistance, the frequency of diseases, including tumors, decreases; the speed of growth of primary tumors and metastases decreases, patient life expectancy increases [2, 15]. These data give ground to state that parameters of earth atmosphere on the height 1700-2200 m above sea level correspond more with standards of energy exchange of the majority of healthy people, moreover, of sick man, than the same ones of atmosphere on the sea level. Such conditions contribute to the permanent overpressure and untimely deterioration of antioxidant systems of organism with negative consequences, especially during dysadaptation. It may be supposed that last are the result of evolutionary “decelerating” of development of antioxidant, human antihypoxic and antiperoxide systems in response to increase of oxygen in atmosphere.

Total hypoxia of tissues accompanies wide range of diseases, being adaptive response to the inspired air of environment, unacceptable for organism, in presence of pathological process. In such organism are changed many physiological, immunological, hormonal and biochemical parameters. Indeed, total hypoxia of tissues in organism at tumor process realizes in the result of narrowing or switching off from functioning of part of capillaries in consequence of their defectiveness and constringtion effect [2, 15], as well as in the result of decrease of flow rate of bloodstream, decrease of total mass of erythrocytes, increase of activity of antioxidant protection (superoxide dismutase, glutathione peroxidase, peroxisomal oxidases, synthesis of ceruloplasmin and other enzymes) [11].

Mentioned data allow to state that occurrence of tumor disease and many other diseases causes the essential changes of interaction between organism and environment [2, 9]. For this reason, search for effective means of treatment of patients with malignant tumors should be based not only on taking into account the connections in known system “organism – tumor” [19], but also in complicated triad “tumor – organism – environment”, i.e. it should be carried out on the basis of holistic, adaptive approach with taking into account regulation of psychosomatic adaptation [20]. Presence of malignant tumor (as, probably, also other
pathological processes) causes the alteration of psychosomatic factors, metabolic processes and regulative systems of organism, alteration of its homeostasis. At that parameters of environment become inadequate concerning the new state of organism of patient. There is reason to think that many diseases, in essence, are manifestation of such dysadaptation determining their essential features, severity and duration. In particular, dysadaptation to environment is obligatory component of pathogenesis of any disease, and in series of cases also its real manifestations. Most probably that dysadaptation is non-specific sign of many diseases, what has emphasized as early as 1937 by A.D. Speransky [21].

Based upon this assumption, one may think that recovery is achieved not only in case, when adaptive responses of organism of patient normalize his interaction with environment, but also environment again becomes adequate for organism (physiologically comfortable). Since severity of disease answers the degree of dysadaptation, which causes series of pathological disorders, the ability of recovery will be determined by that, whether organism of patient with the help of treatment or without it can realize necessary adaptive mechanisms [15, 21, 22].

Inducted by malignant tumor changes of water-structure homeostasis of organism [24], disorders of antioxidant systems decrease total energy-exchange of organism of patient [25] that, in turn, causes the inconsistency of its parameters with environment. At that normoxic atmosphere becomes for patient hyperoxic; earlier normal gravitation – redundant; decrease of intensity of energy-exchange causes the decrease of ratio power-inputs/body mass of patient; compensated by healthy organism influences of geomagnetic and alternating technogenic electromagnetic fields (which have significantly intensified recently), obviously, also decrease activity of functioning of regulatory, adaptive systems of organism and in series of cases at tumor process they become noncompensable.

On the basis of above stated, it may be supposed that for elimination of two factors of dysadaptation organism of patient with tumor includes appropriate adaptive responses. Delivery of oxygen to cells decreases and their breathing changes (total hypoxia of tissues), motion activity decreases (redundancy of motion activity accelerates tumor growth) [26]. Whether accommodation of organism to the third factor of dysadaptation (“electromagnetic smog”) takes place or not, is still not known, though majority of people are living in anomalous geomagnetic and technogenic electromagnetic zones of Earth and often experience significant negative impact, which causes the occurrence of different diseases.

In case, when development of adaptive responses of organism reaches adequate level, malignant cells or “tumor embryo” do not progress, disease does not develop. Already available neoplastic cells die under the influence of immune and non-specific system of resistance of organism or undergo differentiation [27].

It is known that at action of defense mechanisms of cell of “sleeping tumor” in healthy organism may be preserved in latent state for a long time [28].

K. Tepperwein states that in man, whose organs and tissues consist of 60-100 trillion cells, daily are dividing 100 million of cells, 200,000 of which have signs of malignancy [29]. However, malignant neoplasms arise not much as in 20% of human population.

At study of results of postmortem examination of 2238 aged patients malignant tumors have been detected in 1152 cases [30]; at that in 314 patients there were no tumors diagnosed during the life and any clinical signs of tumor disease have not been detected.

It has been showed that growth inhibition and resorption of transplantable tumors in animals has been registered only in those cases, when it was possible to provide changes, typical for intensive reactions of “training” and adaptation, in them without use of cytotoxic drugs [31]. Results of these studies allow to assume that low frequency of self-recovery at tumors in animals and humans is conditioned, first of all, by low level of natural adaptive opportunities.

V.P. Kazachentsev assumes that high speed of intensification of frequency of human malignant tumors is conditioned by permanent decrease of his adaptive capabilities connected with increase of quantity of internal “breakdowns” in organism and fast contamination of environment [22]. Ignoring nature, man begun to live in unacceptable environment, which he has created by his negative activity. Impact of anthropogenic aggressive factors on man generates “cancer background” in patient organism, which causes the occurrence of malignant neoplasms.

High antitumor resistance of animals – “nullers” is well known. Apparently, it is provided by extremely high adaptive flexibility, initial reactivity [15] and may depend on body type of animals [23], determining their “sprinter” response to the inadequacy of organism to the factors of environment. With some confidence we may assume that most essential distinction of tumor processes from sharp infectious disease lies in their chronic course and insignificant protective role of hormonal immune mechanisms. Malignant tumor intensifies initial reactivity, causing the gradual decrease of adaptive abilities of organism (the energy-informative mechanisms, oxygen, hormonal, water-structure homeostasis, etc.). All these factors condition impropriety of adaptive responses of nervous system and other regulating systems [24]. Probably, use of certain complex of impacts on hypothalamus, central nervous system may cause the intensification of adaptive responses of organism, apoptotic death of tumor cells, growth inhibition of malignant tumors or their resorption [15, 31].

On the basis of results of our studies [2] and available data [3, 5] on the role of total hypoxia of tissues and adaptive responses of organism in occurrence and development of tumor disease seems to be perspective the use of drugs in low doses for treatment
of patients with tumors upon the conditions of changing internal medium of organism and environment. Such principles are coherent with the main regulations of homeopathy and antihomotoxicology. Analyzing latter [32–34], we may come to conclusion that homeopathic concepts “vital force” and “vital energy” [32] are in some sense adequate to the concept “adaptive abilities of organism”. If basing on such notions, then main signs of disease (or symptoms) are the external manifestation of adaptive efforts of organism aimed to match its new pathological status the conditions of environment. Acute transitory clinical course, which is typical for infectious diseases, means fast and full realization by organism of adaptive responses, which are expressed in fullness and intensity of symptoms of disease, causing, at the end, recovery. It is conditioned by the fact that organism of patients becomes fully adapted, since preservation of homeostasis is unacceptable background for development of one or another pathology [32]. Presence of dysadaptation is important pathogenic factor, which determines any disease [15, 22].

At the same, chronic clinical course is conditioned by incompleteness of adaptive response of organism of patient to the environment. For such clinical course are typical weakened reaction of organism and, correspondently, vague symptoms. It may be assumed that duration of period of recovery both at acute and chronic character of disease is close to the duration of stage of short-term adaptation of organism of patient.

Use of drugs causing the same symptoms, as disease itself [32], i.e. realization of the main principle of homeopathy is, in essence, factor, which contributes the overcoming of pathological reactivity and helping organism to realize complex of adaptive responses to the environment to a greater extent. In this case homeopathic drugs may be evaluated as adaptogens [35].

Principle of likeness [32, 33] is reasoned and quite perspective, if to be analyzed basing on the notions of adaptive therapy. From this position, important are also other regulations of homeopathy: pathological process occurs only in organism, which is dysadapted [21, 36], and homeopathic treatment eliminates not pathology itself, but normalizes “vital force”, brings homeostasis of organism in state, which is inconsistent with pathology. Last notion coincides with notions of A.D. Speransky [21] and is confirmed by later studies [37].

Homeopathic treatment lies in choice of effective complex of adaptogens, which take into consideration constitution of patient, character and stage of pathological changes, which determine the state of resistance of organism [23, 32, 33]. Our interpretation of the main principles of homeopathy in some way differs from known treatment [33]. It supposes that irritators, which cause responses of organism, come from environment, and homeopathic drug only eliminates factors, which limit these responses in organism. Recovery realizes through the results of adaptation of organism to the environment under the impact of homeopathic drugs.

It should be emphasized that stated hypothesis of use of principles of homeopathy in treatment of tumor disease substantiates also certain limited nature of its possibilities. In neglected stages of malignant process, even at treatment by effective drugs, realization of necessary adaptogenic reactions may turn out to be insufficient. It is conditioned by presence of essential morphofunctional changes and constitutional adaptive limitations of organism in consequence of influence of some factors of environment. Such limitations are pointed out also by data [15], which are the evidence of impossibility to call the necessary adaptive responses in some animals even in the initial stage of tumor progression or in the majority in neglected stages. Moreover, “price for adaptation” may bring the impact of homeopathy to nothing [22].

The limitation of homeopathy opportunities conditions the necessity of analyzing of perspective or antipatic or integrative treatment [32]. According to our concept, disease is induced, and more often intensified by pathological process of dysadaptation of organism, and its symptoms are the signs of adaptive response of organism to inadequate parameters of environment. Basing on it, adaptation may be simultaneously induced by different ways: homeopathic (with the help of intensification of adaptive responses of organism) and antipatic (favorable changes of environment parameters). Such integrative approach decreases necessary adaptive tension, as well as price for adaptation to external factors.

It should be noted that favorable impact of external hypoxic conditions (interval normobaric hypoxia, breathing with the help of Frolov’s Respiratory Training Device, staying of patient in highlands and so on) on the state of organism of patient, including also at tumor process, is variant of antipatic therapy. Replacement of in fact “hyperoxic” respiratory medium by “normoxic” eliminates necessity of appropriate adaptive response of organism of patient. Use of such integrative therapy helps to decrease adaptive tension in organism of patient, to approximate its homeostasis to the state of «rest». Drug therapy carried out against such background, including also antitumor therapy, may turn out to be more effective, since it solves less hard adaptive tasks of organism.

Also may be presented our and available data that modern achievements of nanotechnology give opportunity to use ferromagnetic nanoparticles of iron as antihypoxants. Entering through cellular membranes, these particles interact directly with DNA, causes development of oxygen stress, increase radical forms of oxygen and nitric oxide, strengthens immune mechanisms, increase disintoxication functions of organism of patient, normalize bioenergy and cellular metabolism in different tissues of organism at tumor process. This, at the end, causes destruction of tumor cells and suppression of neoplasm growth. Such changes were obtained by us at peroral use of iron ferromagnetic nanoparticles in experimental animals and patients with malignant neoplasms [38].
In contrast to traditional methods, which study human organism on genic, molecular, cellular and organism level, usually, ignoring external factors of environment, giving the main significance to the drugs, integrative therapy is based on fundamentally another basis taking into consideration complex of internal and external factors of impact on organism of patient. Homeopathic, immunomodulatory or adaptive means (like ferromagnetic nanoparticles) at such antipatic treatment turned out to be quite effective.

Represented data are the evidence that integrative approach may turn out to be successful at treatment of tumor disease. We presume that current among oncologists view about ineffectiveness of treatment of patients with malignant tumors by low doses of non-cytostatic drugs is conditioned by inadequate evaluation of its opportunities and insufficient knowledge of general cause-effect relations at carcinogenesis. This exactly makes doctors apply conventional (proved) drugs in antitumor chemotherapy. However, gathered and analyzed by H.Morgan and coauthors [39] statistical data concerning effectiveness of chemotherapy in cancer patients with III-IV stage in Australia, Canada and USA have showed on the large sampling null five-year survival rate at pancreatic cancer, prostate gland cancer, urinary bladder, kidney cancer, soft tissues sarcoma, melanoma, multiple myeloma. At treatment of other forms of cancer, five-year survival rate has constituted from 0.7 to 3.0%. Authors consider question concerning change of principles of treatment of patients of oncological profile extremely relevant.

We hope that discussion, which concerns presented in this work original approach to the treatment of oncological patients, shortens distance between traditional methods and integrative therapy that will allow to increase effectiveness of treatment of tumor disease.

REFERENCES
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