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Full Length Research Paper

Psycho-immunological treatment of complex cancer patients suffering from psychogenic therapeutic history

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The aim of this work is approbation of the pathogenetically substantiated psycho-immunological rehabilitation of advanced cancer patients with psychogenic medical history. 17 advanced cancer patients (with 6 various types of cancer) took part in this study. All psycho-emotional disorders were diagnosed clinically and psychometrically (SCL 90). The treatment of signs and symptoms of mentioned disorders included hypnotherapy and psychotropic drugs. The specific anti-tumor activity of the immune system was assessed by the delayed type hypersensitivity skin reaction on the tumor-associated antigens. An activation of specific anti-tumor immunity was provided only after stable clinical effect of psycho-correction by specially developed methods of epicutaneous and modified extra-corporeal activation. The effective treatment of psycho-emotional disorders had a direct correlation with spontaneous increase in specific anti-tumor activity of the immune system ($p < 0.0008$). The catamnesis showed that only 5 advanced cancer patients, who were provided with whole course of psycho-immunological rehabilitation survived for 1.5 years and up to 7 years after psycho-immunological rehabilitation. The rest 12 patients died. This study showed some clinical opportunities of positive influence of special psycho-immunological rehabilitation on to the course of a disease of advanced cancer patients with psychogenic medical history.

Key words: Advanced cancer, anti-tumor immunity, cancer rehabilitation, psycho-emotional disorders, psychogenic medical history.

INTRODUCTION

Advanced cancer is the malignant disease that has spread to other places in the body and usually cannot be cured or controlled with treatment. Treatment and care of advanced cancer patients are focused on the manage-ment and relief of symptoms, improving the patient's comfort and quality of life. Actually, such patients are given symptomatic treatment. At the same time, the status of anti-tumor immunity is being a key link in the carcinogenesis chain of advanced cancer. That means the anti-tumor immunity could be considered as the target for pathogenically justified immunorehabilitation treatment. It is also known that the activity of anti-tumor immunity determines survival of patients with cancer. It should be mentioned that an active development of immunotherapy as the mean of immunorehabilitation of compromised immunity of patients living with cancer had promised drastic changes in the management of cancer as well as an increase in survival of patients living with cancer. However, these expectations have not been fulfilled so far. Clinical studies show that initially compro-mised anti-tumor immunity of patients living with cancer cannot be surely recovered by means of immuno-rehabilitation. At the same time, usage of immunotherapy of some patients could not only be useless, but dange-rous due to possibility of stimulation of cancer develop-ment for example through induction Treg cells (Curiel, 2007).

At first sight, an idea of administering pathogenically justified immunorehabilitation to the patients with advanced cancer seems to be inappropriate and even absurd. It could be accepted if to look on the immunorehabilitation from deterministic positions of cell/molecular and/or genetic levels.

The systemic view of holistic approach suggests mandatory taking into consideration the state of higher nervous activity (mental state), which provides serious influence on development and outcome of cancer disease. For instance, depression is alarming the potentially short life of patients living with cancer (Onitilo et al., 2006). In this regard, we assumed that some patients with advanced cancer suffer from psychogenically determined immunosuppression as an outcome of untreated psycho-emotional disorders which have occurred before diagnosis of cancer. Actually, those patients went through massive psycho-traumatic events which were added up by massive stress connected with first time diagnosis of cancer. We also assumed that immunorehabilitation of advanced cancer patients with a psychogenic medical history should be preceded with effective correction of psycho-emotional disorders in order to avoid psychogenic immunosuppressive influence. The objective of this work is development and implementation of psycho-immunological rehabilitation of advanced cancer patients with psychogenic medical history.

Theoretical justification for psycho-immunological rehabilitation of advanced cancer patients with psychogenic medical history

Nowadays, there is no doubt that the immune dysfunctions are the backbone of the tumor pathogenesis. This immune dysfunctions at the same time with destruction of the cellular genetic apparatus in the malignant cells appeared in the form of the cell component of the immune system dysfunction along with malfunction of cell control and cell differentiation mechanisms, immune tolerance and inability to provide effective immune response to developing tumor (Finn, 2008; Prendergast, 2008). In this connection, it was logical to use the wide range of immunotherapy methods in modern oncology. Despite that it was a new step in malignant tumor treatment, it has not solved the problem of its effective treatment (Nedospasov and Kuprash, 2007; Harada and Yonemitsu, 2011). At the same time, laboratory and clinical trials have proved tied and multifunctional interconnections between two most important integrative systems of the human organism which are the immune and the nervous systems (Hall et al., 1985; Pert et al., 1985; Ader and Cohen, 1985), that formed the base for development of modern scientific trends which are the psychoneuroimmunology and psychoimmunology of cancer (O'Sullivan et al., 1994).

The conclusions of the scientific research on influence of chronic psycho-emotional stress (CPES) to an organism of healthy and unhealthy individuals, including those with cancer are most interesting from the practical approach point of view. Nowadays, the somatic outcomes of CPES are well known. So the CPES is able to damage the cell's DNA and inhibit DNA reparation by activation of endogenous mutagens, which are the reactive species of oxygen and nitrogen that forms genome instability (Dimitroglou et al., 2003; Gidron et al., 2006). CPES is always followed by immunosuppression, decrease of quantity and cytotoxic activity of CD8+ and NK-cells and dysfunction of their supervising functions, processes of apoptosis, activation of proinflammatory cytokines and sustentation of not cropped areas of chronic inflammation (Segerstrom, 2005; Lutgendorf et al., 2005; Cohen et al., 2012). All mentioned cases leads to concentration of malignant cells in the body with increase of their invasive potentiality (Sood et al., 2006). CPES adjoints with high risk of development, progress and recurrence of malignant tumors, and the high mortality rate of cancer patients (Thaker et al., 2006; Reiche et al., 2005). The CPES also leads to hippocampal neuronal degeneration as well as to amygdala atrophy (Conrad, 2006), prolonged hypoactivity of the hypothalamo-pituitary-adrenocortical axis (Tsigos and Chrousos, 2002), and accelerated aging of human body (Simon et al., 2006). So, extensive and deep somatic damaging effect of CPES suggests a significant role of psychogenic factors in the development, recurrence and progression of cancer disease in some cancer patients with psychogenic medical history.

On the basis of the above, it is logical to assume that it is difficult to eliminate the factors compromising the immune system due psychogenic influence and suppression of anti-tumor immunity without effective elimination of persistent tonic descending influences of the central nervous system and the higher nervous activity to the body of cancer patients with psychogenic medical history. Confirmation of dependency of anti-tumor immune activity from higher nervous activity is presented by us as a phenomenon of spontaneous increase of anti-tumor activity of the immune system after the effective relief of psycho-emotional disorders in cancer patients with a psychogenic medical history.

Therefore, advanced cancer patients with psychogenic medical history require a special pathogenetically grounded psycho-immunological recovery in order to restore mental condition, to increase quality of life, to activate an anti-tumor immunity and to block the progression of cancer. The main content of psycho-immunological recovery consists of compliance with a strict sequence of two stages of rehabilitation, which are the phase of psycho-correction and the phase of immunomodulation. The main objective of the first stage of rehabilitation (phase of psycho-correction) is an effective and sustainable elimination of CPES effects which

Table 1. Characteristics of advanced cancer patients (n = 17).

Patient №	Age	Sex	Cancer types	Primary tumor localization	Metastasis localization	Stage	Comorbidities	Treatment
1	42	F	Melanoma	Right shoulder	Brain	IV	-	SUR, CHT
2	29	F	Melanoma	Anterior chest wall	Liver	IV	-	SUR, CHT HYP
3	47	F	Melanoma	Anterior abdominal wall	Brain	IV	Urinary stone disease	SUR, CHT
4	43	M	Melanoma	Uveal	Liver	IV	-	SUR, CHT
5	46	F	Melanoma	Back skin	Porta hepatis	IV	Hypertensive heart disease	SUR, CHT
6	51	M	Melanoma	Anterior abdominal wall	Subcutaneous hands and feet	IV	Chronic cholecystitis	SUR, CHT
7	38	F	Melanoma	Skin of temporal region	Retroperito-neum	IV	-	SUR, CHT
8	53	M	Melanoma	Back skin	Subcutaneous hands and feet	IV	Stomach ulcer	SUR, CHT
9	55	F	Melanoma	Neck skin	Supraclavicular and axillary lymph nodes	IV	-	Refuse standard treatment
10	76	F	Kidney cancer	Right kidney	Both lungs, mediastinal and neck lymph nodes, ribs	IV	Hypertensive heart disease, coronary artery disease	SUR, CHT
11	58	F	Kidney cancer	Right kidney	Left kidney	IV	Hypertensive heart disease	SUR, CHT
12	53	F	Stomach cancer	Stomach	Porta hepatis	IV	-	SUR, CHT
13	28	M	Stomach and pancreas cancer	Stomach and pancreas	Paraaortic lymph nodes	IV	-	SUR, CHT
14	50	F	Breast cancer	Left breast	Skull, ribs, sternum, clavicles, spine, pelvis	IV	-	SUR, CHT, RT
15	54	F	Breast cancer	Right breast	Ribs, shoulder joint	IV	Hypertensive heart disease	SUR, CHT
16	45	F	Ovarian cancer	Right ovarian	Mediastinal lymph nodes	IV	-	SUR, CHT
17	48	F	Lung cancer	Right lung	Left lung	IV	-	SUR, CHT

SUR – surgery; CHT – chemotherapy; RT – radiotherapy; HYP – hyperthermia.

appear in different psycho-emotional disorders such as anxiety and depression. The main objective of the second phase of recovery (phase of immunomodulation) is the activation of specific anti-tumor immunity.

METHODOLOGY

This study had local Ethical committee approval (the Ethical committee of the Institute of Clinical Immunology, Siberian Branch, Russian Academy of Medical Sciences, Novosibirsk, Russian Federation, protocol № 29, August 18, 2004). All patients gave written informed consent.

Characteristics of cancer patients

The special psycho-immunological rehabilitation has been offered to 17 patients with advanced cancer (13 women and 4 men). These patients during 5 years (2007 to 2012) had been selected by us among other cancer patients on the following criteria: (1) the progression of the disease, despite that the ongoing standard combination therapy of cancer was provided, (2) the presence of distant metastases (stage IV of cancer), (3) the obvious massive psychotrauma occurred in the lives of patients before being diagnosed with cancer (psychogenic medical history), and (4) informed consent of cancer patients for carrying out rehabilitation. The special clinical case was associated with the patient number 9 (Table 1), who strictly refused to hold a standard combination therapy of cancer, but expressed the strong desire to do her psychological and psychothera-peutic aid. An individual characteristic of cancer patients is presented in Table 1.

Psychogenic medical history investigation

Psychogenic medical history has been studied by us in the clinical trial for each patient in medical history of the disease (anamnesis morbi) during first visit to the patient and included the presence of massive psycho-traumatic events (death of the close person, divorce, frequent family conflicts, change of residence, work and appearance of the disabled person in family) with the formation of helplessness and despair.

The mental status examination

The mental-status examination of cancer patients was conducted by the psychiatrist with supplemental usage of all the following psychometrical test systems (for example, The Symptom Checklist 90 (SCL-90) and rates: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, global severity index). The psychiatrist detected the presence or absence of mental disorders in cancer patients in accordance with International Classification of Diseases (ICD-10). Normal values of SCL-90 parameters for healthy people are presented in Table 2 (Tarabrina, 2001). The mental-status examination was administered on the following stages of research: “Before” – before psycho-correction, “After” – after hypnotherapy session and “1 month later” – 1 month later hypnotherapy sessions.

Table 2. Psychometrical indicators (SCL-90) and DTH skin reaction on TAA in advanced cancer patients before, after and 1 month later after completion of HSP sessions (n = 17).

Indicators	Normative values†	Comparative analysis "before-after" and "after -1 month later"				
		Before (B) mean±SEM	After (A) mean±SEM	1 month later mean±SEM	P B-A	P A-1 mon.
Somatization	0.44±0.03	1.31±0.16	0.67±0.12	0.79±0.15	0.0001	*
Obsessive-compulsive	0.75±0.04	1.14±0.12	0.62±0.10	0.76±0.11	0.002	*
Interpersonal sensitivity	0.66±0.03	1.12±0.20	0.53±0.10	0.63±0.11	0.006	*
Depression	0.62±0.04	1.45±0.16	0.54±0.09	0.84±0.12	0.0002	0.004
Anxiety	0.47±0.03	1.10±0.15	0.35±0.09	0.49±0.09	0.0002	*
Hostility	0.60±0.04	0.74±0.12	0.32±0.07	0.43±0.08	0.007	*
Phobic anxiety	0.18±0.02	0.55±0.14	0.23±0.08	0.23±0.07	0.045	*
Paranoid ideation	0.54±0.04	0.73±0.16	0.43±0.12	0.50±0.14	*	*
Psychoticism	0.30±0.03	0.67±0.11	0.31±0.07	0.41±0.08	0.0006	*
Global severity index	0.51±0.02	1.06±0.12	0.48±0.07	0.61±0.10	0.0002	*
DTH skin reaction on TAA, mm	not defined	4.59±1.52	11.4±2.45	7.35±2.06	0.0008	0.003

Mean ± SEM – means and standard errors means; *P > 0.05; † - Normative values for healthy people (Tarabrina, 2001).

Correction with medicine of psycho-emotional disorders

The medicamental correction of mental disorders with medicine in advanced cancer patients had been conducted immediately after diagnosis. The antidepressants (tianeptine, venlafaxin), anxiolytics (afobazolum, microdoses of diazepam) and their combination were used. The psychotropic drugs were prescribed for a period of 3 to 6 months to enhance and prolong the therapeutic effect of hypnossugestive psychotherapy (HSP).

Method of hypnossugestive psychotherapy

The method of hypnossugestive psychotherapy is based on strict successive, interconnected, figurative, pathogeneticaly substantiated suggestive influences in hypnotic states. This method includes followed sessions: (1) Establishment of hypno-rapport between patient and physician; (2) hypnotic de-actualization of psycho-traumatic emotions and experience including a fact of cancer diagnosis; (3) hypnotic lockout of dreams connected with known stress situations which are regularly reproduced in the sleep with the corresponding psycho-vegetative reactions. It is needed for the subject's exhaustion of psychogenic disorders and to prevent their lingering course; (4) hypnotic reproduction of a personal "health standard" or "health syndrome" – a key session of the whole course of HSP. This "syndrome" is based on using widely known phenomenon of hypnotic hypermnesia (increased memory under hypnosis) generally used for restoration of psychogenic abnormalities of memory. However, it is possible to restore memory of heart beat, respiratory rate, glycemic rate, enzyme reaction activity, and stereotype of digestive system functions from a specific time in the past. The patient recollects the concrete day (date, month, year) from the past – "model, standard" of his health when there was no tumor and he felt well, mentally and physically. In a hypnotic state, suggestions were conducted using the images that are required to retrieve from the memory of cancer patients the "records" that are well known to the body as "health standard". It should be noted that in this key session HSP hypnotic suggestions related to the activation of a great desire, the need for further self-realization in their lives were conducted. In fact, these suggestions were aimed at restoring the loss of life purpose dominant; (5 to 6) the last HSP sessions focused on patients' education in autohypnosis under suggestive influence. Then patients were given detailed instructions to use autohypnosis for prolongation of the medicinal effect, as well as keeping psychic and vital tone of cancer patients. The duration of the individual course of the HSP was 14 to 16 days.

Evaluation of specific anti-tumor activity of the immune system in advanced cancer patients

Anti-tumor activity of the immune system was assessed by skin test of the delayed type hypersensitivity (DTH) reaction on the tumor-associated antigens (TAA), which were used as a lysed human melanoma cell line BRO (Lockshin et al., 1985) in the amount of 25 thousand cells in a test. Human melanoma cell line BRO was obtained at the Institute of Cytology of Russian Academy Sciences (St. Petersburg, Russia). We investigated the DTH skin reaction after the intradermal administration on the forearm at 9, 12 and 24 h, to identify the peak responses. The peak response in most cases (the diameter of redness in mm) was observed after 12 h. Selection of human melanoma cell line BRO was determined by need to use in one test, the maximum range of TAA to assess the anti-tumor activity of the immune system of patients with different cancers. As shown, there are all kinds of TAA characteristic of solid tumors on the melanoma cells (Wang, 1997).

Selection of the minimal quantity of TAA for the DTH skin test (according to our preliminary studies) was used in order to obtain physiological (not stimulated) specific anti-tumor immunological response as well as in order to exclude the possibility of vaccine's effect of the diagnostic test itself. In comparison with our colleagues, who used the DTH skin reaction on TAA of human melanoma cell lines in the study of clinical efficacy of anti-tumor polyvalent vaccine "CancerVax" (developed from three allogeneic human melanoma cell lines) (Habal et al., 2001), we used a diagnostic dose which was nearly 100 times smaller (2.5×10^4 cells versus 2.4×10^6 cells). In addition, our patients did not receive any immunotropic therapy during the study. The selected dose does not cause allergic and other pathological reactions. It is known that the delayed type hypersensitivity reaction is a specific immune response and begins to manifest in 8 to 12 h after ingestion antigen and in most cases the reaction reaches a peak after 48 to 72 h (Carroll, 2011). In our case, the peak responses which is due to the

absence of prior immunization of cancer patients and is the largest contribution of cellular reactions in the DTH skin test were achieved early (within 12 h) (Jacysyn et al., 2001). Evaluation of a specific anti-tumor activity of the immune system in advanced cancer patients was conducted through the research stages: “Before”, “After”, and “one month later”.

Preparation of tumor associated antigens for diagnostic test - DTH skin reaction

The lysed cells of the human melanoma cell line BRO were used as the TAA for diagnostic test. The human melanoma cell line BRO were maintained in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, L-glutamine (2 mmol/ml), 25 mmol (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES buffer), and 25 µg/ml gentamicin at 37°C in 5% CO_2 humidified air. Cells were detached from the dish by treating with trypsin-ethylenediaminetetraacetic acid (EDTA) followed by washing three times with Dulbecco’s phosphate-buffered saline, precipitated by centrifuging, counted and diluted with 0.9% saline solution with 0.1% EDTA. Cells were lysed by repeated (8 times) freezing and stored at -80°C until use. As diagnostic test, 2.5×10^4 lysed cells line BRO in 50 microliters was used.

Preparation of tumor associated antigens for epicutaneous activation of specific anti-tumor immunity

The lysed cells of the human melanoma cell line BRO were used as the TAA for epicutaneous activation of specific anti-tumor immunity. The human melanoma cell line BRO were maintained in RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum, L-glutamine (2 mmol/ml), 25 mmol HEPES buffer, and 25 µg/ml gentamicin at 37°C in 5% CO_2 humidified air. Cells were detached from the dish by treating with trypsin-EDTA followed by washing three times with Dulbecco’s phosphate-buffered saline, precipitated by centrifuging, counted and diluted with 0.9% saline solution with 0.1% EDTA. Cells were lysed by repeated (8 times) freezing and stored at -80°C until use. The one epicutaneous activation of specific anti-tumor immunity was performed with usage of 2.5×10^6 lysed cell line BRO in 0.5 ml.

Preparation of tumor associated antigens for extracorporeal activation of specific anti-tumor immunity

The lysed placental cells of domestic pig were used as the TAA for extracorporeal activation of specific anti-tumor immunity. They were obtained by careful mechanical homogenization of placenta without trypsin. Cells were diluted in saline solution supplemented with 0.1% EDTA and 25 µg/ml gentamicin up to concentration of 50×10^6 placental cells in 1.0 ml. Cells were lysed by repeated (8 times) freezing and stored at -80°C until use.

Extracorporeal activation of specific anti-tumor immunity

A peripheral blood mononuclear cell (PBMC), separated from 25 ml of heparinized cancer patient blood have been diluted in RPMI 1640 and supplemented with 20% autological plasma, L-glutamine (2 mmol/ml), 25 mmol HEPES buffer, and 25 µg/ml gentamicin. PBMC in concentration 4×10^6 cells/ml have been placed in cell culture dish in proportion 1 to 2×10^6 cells/m^2. The lysed placental cells of domestic pig were used as the antigen in proportion 1/6 (lysed cells of pig placenta/PBMC). This proportion was found as optimal in previous research. Further PBMC with added antigen were placed into CO_2-incubator and incubated at 37°C in 5% CO_2 humidified air. The incubation time was 6 to 8 h for antigen processing by monocytes of PBMC. The PBMC had been collected after completion of incubation by rubber policeman and have been triple-washed in the phosphate buffer solution with added 5% autological plasma of cancer patient. The washed incubated PBMC were diluted in 2 ml of autological plasma of cancer patient and shared among two 1 ml syringes. Incubated PBMC were administered subcutaneously in subscapular fossa area and in the area of lower abdomen laterally from umbilicus (palm width sinistral or dextral). Totally three procedures were provided, second provided after two weeks, and the third one after one month since the first procedure.

Epicutaneous (scarification) activation of specific anti-tumor immunity

The superficial line scarifications were applied after skin disinfection on the area of 4 m^2 with a gap in between lines of 2 to 3 mm wide by blood lancet (scarificator). Damaged area was covered by sterile patch underneath which by syringe was administered a solution with TAA (2.5×10^6 lysed cells line BRO in 0.5 ml). The subclavicular and subscapular areas were used for epicutaneous application of TAA. The exposition of patch with TAA solution left was for 3 days. Four sessions of epicutaneous activation of specific anti-tumor immunity were administered with 14 days break and three sessions were provided with 30 days break.

Statistical analysis

The statistical data processing was done using “BioStat 2009 Professional 5.8.4”, which is publicly available. The level of statistical significance (so-called alpha level for a p-value) was accepted as 0.05. All parameters of investigation were normally distributed (by Kolmogorov-Smirnov test), so in general the parametric tests were used. In order to compare two independent statistical samples the non-parametric Mann-Whitney test was used. The relationship study between psychometrical (SCL-90) and immunological (DTH skin reaction on TAA) parameters was carried out using Pearson's correlation test.

RESULTS

Mental disorders in advanced cancer patients with psychogenic medical history

Clinical studies of 17 advanced cancer patients with psychogenic medical history showed that 100% had a variety of psycho-emotional comorbidity disorders predominantly of anxiety and depression spectrum disorders. The disorders distribution on the base was of ICD-10: ge-neralized anxiety disorder (F41.1) – 3 (patients № 1, 13, 17), mixed anxiety and depressive disorder (F41.2) – 2 (patients № 4, 6), post-traumatic stress disorder (F43.1) – 1 (patient № 7), prolonged depressive reaction (F43.21) – 4 (patients № 3, 8, 12, 16), mixed anxiety and depressive reaction (F43.22) – 6 (patients № 2, 5, 9, 10, 11,14) and organic anxiety disorder (F06.4) – 1 (patient № 15), which in our opinion was a complication chemotherapy. The results of clinical studies of the mental state of ad-vanced cancer patients in general, have been confirmed by the data of psychometry (Table 2, the indicators “Before”).

Table 3. A comparative analysis of the studied parameters in cancer patients with unstable and stable effect of correction of psycho-emotional disorders.

Indicator	Normative value†	Unstable effect (n=11) mean±SEM	Stable effect (n=6) Mean±SEM	P
Somatization	0.44±0.03	1.05±0.18	0.32±0.13	0.014
Obsessive-compulsive	0.75±0.04	0.95±0.13	0.42±0.15	0.024
Interpersonal sensitivity	0.66±0.03	0.86±0.11	0.20±0.08	0.005
Depression	0.62±0.04	1.10±0.12	0.35±0.11	0.003
Anxiety	0.47±0.03	0.68±0.10	0.13±0.07	0.003
Hostility	0.60±0.04	0.50±0.09	0.31±0.15	*
Phobic anxiety	0.18±0.02	0.33±0.10	0.05±0.03	*
Paranoid ideation	0.54±0.04	0.71±0.18	0.11±0.04	0.009
Psychoticism	0.30±0.03	0.57±0.10	0.12±0.07	0.007
Global severity index	0.51±0.02	0.82±0.11	0.23±0.07	0.004
DTH skin reaction on TAA, mm	not defined	1.91±0.53	17.3±2.55	0.0009

Mean ± SEM – means and standard errors means; *P > 0.05; † - Normative values for healthy people (Tarabrina, 2001).

Psycho-correction stage: Is the first stage of psycho-immunological rehabilitation

The clinical benefits after completion of HSP have been noticed in all advanced cancer patients. It was confirmed by the results of psychometry and comparative analysis, which showed significant improvement in almost all studied parameters (Table 2). Along with a significant improvement in the mental state of cancer patients, a spontaneous increase in specific anti-tumor activity of the immune system has been observed, as determined by DTH skin reaction on TAA ($p < 0.0008$). The sustainability of mental and immunological changes was the main criterion in the decision to move to the next phase of psycho-immunological rehabilitation which is a stage of immunocorrection. In this regard, the studied parameters on the stage "one month later" after completion of the HSP indicated the stability or instability of earlier positive changes. However, in a comparative analysis of indices in the overall group of cancer patients at stages "After" and "one month later" this deterioration was not evident (Table 2). But a careful study of the indicators on the stage "one month later" detected a clear split of cancer patients into two groups by the intensity of DTH skin reaction on TAA (Table 3).

The DTH skin reaction was less than 5 mm in one group of patients, and it was greater than 5 mm in the other group. It was found that cancer patients in these groups differed substantially also in almost all psychometrical parameters. The group of patients with DTH skin reaction less than 5 mm (11 of 17 patients) was characterized by the deterioration of psychometrical indicators, what allowed us to identify this group of patients, as a group with unstable effect of correction of psycho-emotional disorders (patients number 1, 3, 4, 5, 6, 7, 8, 12, 13, 15, 17). Clinically, these patients had worsening of general and mental health, in spite of the use of antidepressants, anxiolytics, and conduct of autohypnosis sessions. Another group of patients whose DTH skin reaction was more than 5 mm (6 patients) differed by maintenance of the previously achieved positive effects of psycho-correction with appropriate psychometrical characteristics. Last group was identified by us as a group of patients with stable effect of psycho-correction (patients' number 2, 9, 10, 11, 14, 16). The close relationship of specific anti-tumor activity of the immune system with the higher nervous activity of cancer patients was confirmed by the correlation analysis between the DTH skin reaction on TAA and psychometrical parameters of SCL-90 on all stages of observation (Table 4).

The dynamics of the relationship showed that medical and psychotherapeutic effect on higher nervous activity of the cancer patients was accompanied by cumulative increase in significant negative correlations between specific anti-tumor activity of immune system and mental well-being of cancer patients. The greatest number of correlations has been observed in 1 month after completion of HSP. Cancer patients with sustained effect of psycho-correction (patient number 2, 10, 11, 14, 16) were proposed as second phase of psycho-immunological rehabilitation (phase immunocorrection), except for patient number 9.

Stage of immunocorrection: The second stage of psycho-immunological rehabilitation

The stage of immunocorrection lasted for 5 months, along with the procedures of activation of specific anti-tumor immunity, advanced cancer patients taking psychotropic medications and performed self-hypnosis sessions. Each procedure of epicutaneous activation of specific anti-tumor immunity was accompanied by local reactions such as redness, pain, and local itching at the injection site. All cancer patients observed pain in the area of metastatic tumor formation (including previously undiagnosed) as well as pain in regional lymphnodes on

Table 4. The correlation analysis between the DTH skin reaction and psychometrical indicators of SCL-90 in advanced cancer patients with psychogenic medical history on stages of observation (n=17)

Indicator	DTH skin reaction on TAA, mm					
	Before		After		1 month later	
	r	P	r	P	r	P
Somatization	0.13	*	-0.40	*	-0.64	0.006
Obsessive-compulsive	-0.27	*	-0.35	*	-0.73	0.0008
Interpersonal sensitivity	-0.09	*	-0.58	0.014	-0.82	0.0001
Depression	-0.09	*	-0.44	*	-0.78	0.0002
Anxiety	-0.10	*	-0.51	0.037	-0.74	0.0006
Hostility	-0.06	*	-0.29	*	-0.51	0.039
Phobic anxiety	-0.16	*	-0.28	*	-0.57	0.017
Paranoid ideation	-0.31	*	-0.37	*	-0.59	0.013
Psychoticism	-0.22	*	-0.53	0.030	-0.66	0.004
Global severity index	-0.14	*	-0.60	0.012	-0.76	0.0003

the 3rd day, sometimes increased body temperature to 37°C, deterioration of health in the form of weakness, lethargy and sleepiness. In order to relief these reactions, patients received Nise (nimesulide) tablets 100 mg, 2 times a day for 5 to 7 days. Procedures of extracorporeal activation of specific anti-tumor immunity also accompanied by systemic reactions, but clinically less severe than with procedures of epicutaneous activation. In addition, local reactions were observed such as redness, pain and itching at the site of local administration.

Catamnesis

The advanced cancer patients with unstable clinical effect of the correction of the psycho-emotional disorders (patient № 1, 3, 4, 6, 7, 8, 12, 13, 15, 17) died within 2 to 5 months since psycho-correction stage had been over, except patient № 5 who had died after one year. These advanced cancer patients are likely to have had more pronounced somato-psychic disorders that were not consistently removed with psycho-correction techniques and failed to have influenced anti-tumor immunity. Among the advanced cancer patients that were subjected to psycho-immunological rehabilitation (patient No. 2, 10, 11, 14, 16) the following results were observed. Patient

№ 2 is alive, catamnesis contains 5 years, a year after the psycho-immunological rehabilitation was over, the symptoms of hemangioma were revealed in the place of liver metastasis (on the basis of the ultrasonic examination data). Patient № 10 is alive; catamnesis was 2 years without substantial negative dynamics. Multiple foci of fibrosis and calcification were discovered by computed tomography. Patient № 11 is alive, catamnesis was 6.8 years after psycho-immunological rehabilitation had finished. A very interesting fact was revealed during the research. After massive stress (she found out about her daughter's drug addiction), the quick development of the cancer disease was observed and within 7 days the size of the metastasis in the only kidney increased from 38 × 23 mm to 41 × 32 mm. After the effective relief of the psycho-emotional disorders, metastasis regression to 12 × 11 mm was observed. Patient № 14 is alive, catamnesis was 1.5 years. Multiple foci of osteosclerosis without negative dynamics were observed (on computed tomography). Patient № 16 is alive, catamnesis was 4 years. Negative dynamics is not observed, pneumosclerosis foci and extensive fibrotic process are observed in the mediastinum (on computed tomography).

Clinical case (patient № 9)

We have observed the unique clinical case of the cancer patient with malignant melanoma who refused to hold mutilating surgery and chemotherapy, but approached us for psychological help. The patient number 9 was 55 years old, and an accountant. In autumn 2004, melanoma localized on the neck on the left, was histologically verified. The patient turned to us on 20th January, 2005. It was examined that the patient had the primary focus (40 × 35 mm) and multiple metastases in the neck (20 mm), supraclavicular (35 mm) and axillary (20 mm) lymph nodes on the left (Figure 1). Ultrasound examination of the primary tumor revealed that the depth of tumor invasion in the tissues of the neck is 25 mm. After examination, the patient was diagnosed a psychogenic medical history (she lives with a disabled husband, who is alcoholic), mixed anxiety and depressive reaction (F43.22) and the lack of inhibition of specific anti-tumor activity of the immune system, defined by the absence of DTH skin reaction on TAA. We observed that the patients with a similar localization of melanoma died within 4 to 6 months due to profuse bleeding from the

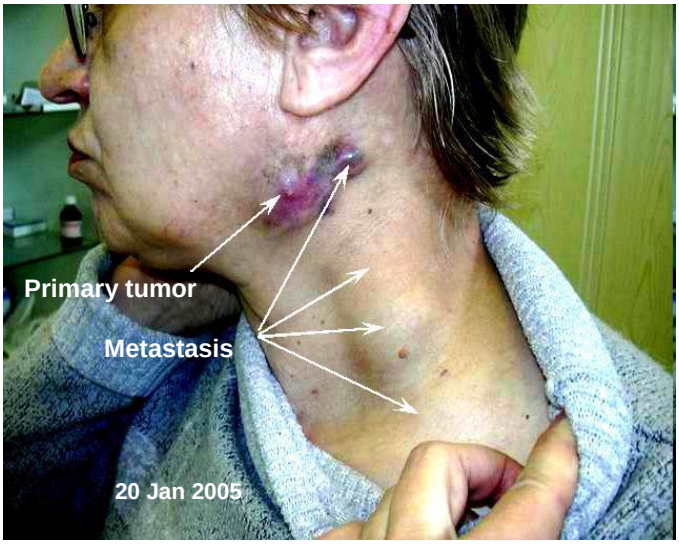

Figure 1. Localization of malignant neck melanoma, patient N9.

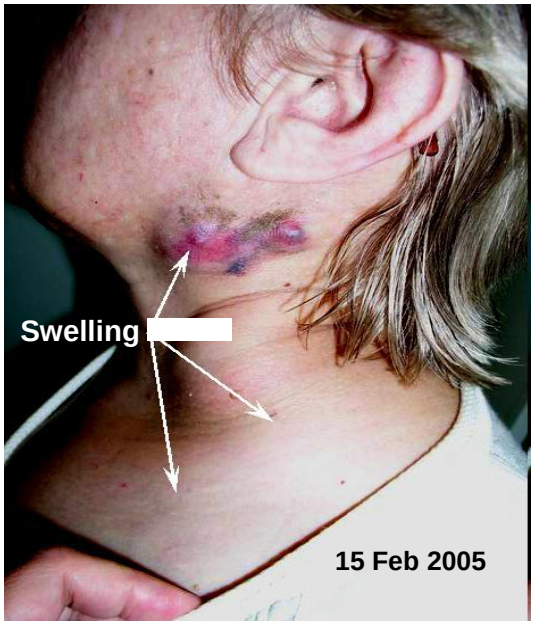

Figure 2. Pronounced swelling of neck tissues after organic-oriented - sessions.

tumor foci and frequent metastasis to the brain. From January 21st to February 4th, 2005, the patient had undergone a course of hypnotherapy consisting of 4 treatment sessions and 2 sessions of self-hypnosis training. After treating the patient with HSP (5th February, 2005), along with the improvement of general state of health and relief of anxiety and depressive disorders, positive changes in a number of objective indicators were seen.

Thus, DTH skin reaction on TAA increased from 15 mm (before HSP) to 40 mm (after HSP) and maintained for 2 days, the absolute number of peripheral blood lymphocytes increased 3 times: from 709 to 1 mm^3 (before HSP) up to 2244 in 1 mm^3 (after HSP). In addition, there was a change of the vegetative (autonomic) nervous system, which was assessed by heart rate variability (HRV) (Task Force, 1996). HRV is the assessment of individual differences in emotional reactions, particularly in relation to social processes and mental health (Appelhans and Luecken, 2006). The indicator of the total power (TP of HRV) at the spectral analysis increased 20-fold: from 213 ms^2 (before HSP) to 4260 ms^2 (after HSP). In addition, there was a reduction of ratio of LF/HF (normalized units) 5-fold: from 2.76 (before HSP) to 0.53 (after HSP), indicating a change of state of sympathicotonia to the state parasympathicotonia and this is a confirmation of the clinical fact of depression relief (Giese-Davis et al., 2006).

After the completion of HSP, the patient conducted daily self-hypnosis sessions in accordance with our proposed program, the content of which was aimed at forming a dense impermeable capsule around the tumor foci, which like a “plaster cocoon walls up, squeezes and strangles tumor foci.” After several self-hypnosis daily sessions lasting 1 h each, the pronounced swelling of the left side of the neck and supraclavicular area with the transition to the chest were observed (Figure 2), body temperature rose up to 38°C, and itching of tumor foci appeared. The patient reported that “stifling of the tumor” started. Within 8 days, the swelling completely disappeared, along with a decrease in the size of metastatic lymph nodes in the neck, supraclavicular and axillary regions. The patient continued, nearly on a daily basis, to use self-hypnosis according to organic-oriented suggestive program “stifling of tumor foci.” Nine months after (03 November, 2005) the beginning of organic-oriented therapeutic autosuggestion, the patient underwent ultrasound examination of the tumor foci.

The results showed regression of metastatic lymph nodes in the neck, in the supraclavicular and axillary regions. A fibrous capsule (Figure 3) was formed deep in the tissues of the neck throughout the borders of tumor invasion of primary tumor focus, which actually corresponds to the content of curative autosuggestion. Further observation showed that endophytic growth of the primary tumor focus changed to exophytic growth (tumor acquired an exophytic form on the leg with a base of 23 mm) with the regression of metastatic lymph nodes in the neck, in supraclavicular and axillary regions (Figure 4). Hereinafter, a slow progression of the cancer process with a gradual increase of phenomena cachexia was observed. The patient died on 14th April, 2008. Despite the expected death, it may be stated that the cancer patient had been able to live an active life for 3 years without the operation of the neck melanoma.

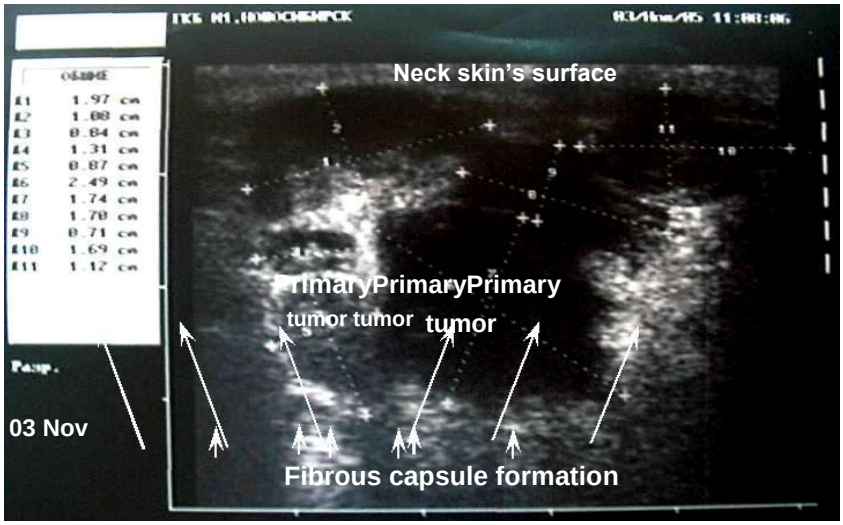

Figure 3. Fibrous capsule around the primary tumor in the depth of the tissues neck after self-hypnosis sessions (ultrasound data).

Figure 4. Exophytic growth of melanoma with metastases regression in the lymph nodes of the neck and supraclavicular area against self-hypnosis treatment sessions.

DISCUSSION

The peculiar properties of mental disorders in advanced cancer patients with psychogenic medical history

The study of psychogenic medical history showed that all patients were in the state of obvious emotional stress before cancer diagnosis (in average of 1.5 years), which was caused by massive psycho-traumatic events. This is a long-term emotional tension accompanied by the formation of the feeling of helplessness, hopelessness, despair. We can assert that these future cancer patients long before the diagnosis of cancer have already had psychogenically caused psycho-emotional and psychosomatic disorders. The diagnosis of cancer itself is an additional massive and inexhaustible psychotrauma, emotionally paralyzing fear, so-called "Damocles syndrome" (Koocher and O'Malley, 1981).

The cancer patients with psychogenic medical history are patients with doubled massive psychotrauma. Undoubtedly, advanced cancer patients with psychogenic medical history had somatopsychic disorders along with cancer progression, so these patients were observed with clinically difficult to differentiate combination of psychosomatic and somatopsychic disorders. The main feature of psychiatric disorders in cancer patients with psychogenic medical history that we have found is the fact that, despite the urgency of the massive psychotrauma and other conditions for the development of neuroses (known as neurotic "Jaspers' triad"), the cancer patients show the condition which is opposite to neurosis and can be defined as a state of "deneurotization". This phenomenon is clinically manifested by blurry, non deployed and tarnish mental symptoms, and cancer patients themselves do not consider their mental condition as sick and perceive it as quite natural, situationally understandable, though very painful, subjectively. This deneurotization syndrome is hard to define according to DSM-IV or ICD-10.

In addition, some advanced cancer patients are observed with conditions of dissociative disorders that manifest themselves through inconsistency of psychometrical assessments to clinical studies. In other words, the psycho-emotional disorders in a clinical study are obvious, but psychometrical parameters are within the normal limits. The deneurotization and dissociative disorders can insidiously hide the true extent of the level

of psychopathology in advanced cancer patients and may be the cause of undiagnosed mental disorders. Thus, the study of psychiatric morbidity with self-report screening instrument without clinical examination does not provide a fair view of psychopathology in cancer patients.

HSP as a method of choice for the quick correction of mental disorders in advanced cancer patients

For the fastest and effective correction of psycho-emotional disorders in advanced cancer patients, combination approach was selected, which involves the simultaneous use of psychotropic drugs, and hypno-therapy. This approach was driven by the severity of psychopathology of advanced cancer patients and the possibility of rapid progression of the cancer disease. It should be noted that hypnotherapy differs from other methods of psychotherapy by high efficiency and velocity of clinical benefit achievement including oncology (Montgomery et al., 2013). Thus, the comparative analysis has shown that after 600 sessions of psychoanalysis, 38% of patients reported feeling better, after 22 sessions of behavioral therapy, 72% of patients reported a positive result, and after 6 sessions of hypno-therapy, 93% of patients referred to the desired effect (Barrios, 1970). Our 25-years clinical experience confirms the major clinical capabilities of hypnossugestive psycho-therapy in the correction of mental and psychosomatic disorders. In particular, we first discovered the pheno-menon of psychogenic mobilization of CD34+CD38- stem cells (Bukhtoyarov et al., 2006) and an increase in telomere length in peripheral blood mononuclear cells in cancer patients during hypnotherapy (Bukhtoyarov et al., 2008). Later, this phenomenon to some extent has been confirmed by other researchers using psychosocial telephone counseling intervention (Biegler et al., 2012). It should be noted that because of the state of hyper-suggestiveness of advanced cancer patients there is a risk of formation of hypnotic dependence (hypnomania), so the number of HSP sessions was limited to 6 sessions of hypnotherapy.

DTH skin reaction on TAA as a biomarker of removing mental disorders

It can be assumed that the spontaneous increase in specific anti-tumor activity of the immune system, as determined by DTH skin reaction on TAA, reflects a relief of psychogenic immunosuppressive effects of higher nervous activity on the anti-tumor activity of the immune system of advanced cancer patients. Actually, DTH skin reaction appeared to be a kind of biological marker of the presence or absence of psycho-emotional disorders in advanced cancer patients with psychogenic medical history. It can be assumed that the initial absence of correlation between DTH skin reaction and psychometrical parameters likely was caused by the disintegration processes in the organism of advanced cancer patients inter alia by violation of the interaction of the two main integrative systems of the body which are the nervous and immune systems. The systemic impact (medication and psychotherapy) on higher nervous activity in cancer patients is accompanied by gradual recovery of damaged linkages between the nervous and immune systems of the body. These data indicate a sig-nificant effect of the higher nervous activity on to the anti-tumor activity of the immune system of advanced cancer patients with psychogenic medical history.

Features of immunocorrection

The main task of the immunocorrection stage was stimu-lating of the specific anti-tumor immunity of advanced cancer patients by immunological methods after spontaneous increase of their immune system anti-tumor activity as a result of sustained relief of psycho-emotional disorders. Presumably, the effective activation of the specific anti-tumor immunity had to have a positive impact on the course of the cancer disease. Therefore we deliberately developed a method of epicutaneous (scarification) activation of specific anti-tumor immunity and extracorporeal activation method using a small amount of peripheral blood. Both methods in the preliminary studies have shown high effectiveness and safety in clinical practice (unpublished data). It should be particularly noted that the very low dose of TAA, moreover introduced epicutaneous, had led to systemic reactions of the whole body. It can be assumed that such clinical effect was due to the specific systemic immune responses that are associated with the capture TAA by antigen-presenting epidermal Langerhans cells and migration of these cells to regional lymph nodes and antigen-presenting TAA. The latest data shows greater potential of CD8+ cells activation by Langerhans cells (Polak et al., 2012). The antigen-presenting TAA in the lymph nodes leads to activation and clonal expansion of antigen-specific T cells and the subsequent development of specific inflammation in metastatic tumor foci. We observed systemic clinical manifestations of these processes on the third day.

Mind and tumor encapsulation

Scientific and clinical evidence shows that cancer has always been primarily a local tissue process. Ideally, the focus of the tumor should be immunogenic and is supposed to be recognized by the immune system as allogenic and thus, to be localized (delimitated) and destructed by the cell-effectors of specific anti-tumor im-munity. In this case, encapsulation process is a universal

natural mechanism of localization of anything allogenic in the body. This fully applies to the localization of malignant tumor formation. A fibrous capsule of different density around the tumor foci have always been observed in experimental animals. It is interesting that the structure of the extracellular macromolecule matrix in capsules around the malignant and benign tumors do not differ (Grigioni et al., 1990). In clinical practice, we can often see a favorable course of cancer regardless of the tissue localization when dense fibrous capsule around the tumor foci are formed. Actually, the formation of fibrous capsule is associated with low levels of cancer recurrence and a capsule can serve as a mechanical and chemical barrier to metastasis (Lunevicius et al., 2001).

Other authors in clinical practice found that the encapsulation of the tumor was an important favorable prognostic factor for survival without signs of cancer disease (Sherratt, 1999). In this regard, we have developed organic-oriented treatment program for self-hypnosis, which presumably could have a decreased trophic's effect on the tumor tissue and contribute to the induction of tumor encapsulation. The examined clinical case confirms what is known about the significant impact of the brain and higher nervous activity on cancer (Mravec et al., 2008). Furthermore, this case presents new data on the possible trophic effects on the tumor tissue and on suppressing the cancer process by the deliberate action on the higher nervous activity in cancer patients.

The role of the mind in generalization of the cancer process, the phenomenon of "reparative trap"

The cellular and molecular factors and mechanisms of cancer's generalization have been presented in detail nowadays, the determinants of invasiveness and the invasion-metastasis cascade have been studied (Weinberg, 2008), the tumor-induced immunosuppressive network have been shown (Kim et al., 2006). There is also evidence that biobehavioral risk factors such as social adversity, depression, and stress are involved in cancer progression (Lutgendorf and Sood, 2011; Spiegel, 2012). Researchers found a 30-fold increase in cancer spread throughout the bodies of stressed mice, compared with those that were not stressed. Chronic stress acts as a sort of fertilizer that feeds breast cancer progression, significantly accelerating the spread of the disease in animal models (Sloan et al., 2010; Moreno- Smith et al., 2010). It can be argued with a certain degree of confidence that chronic stress is also a kind of fuel for growth and generalization of human cancer.

The results of this study suggest that the decisive role in the generalization of the cancer process for the category of advanced cancer patients with psychogenic medical history is the psychogenic factor. This factor is shown in the form of psychogenically determined mental disorders (depressive and/or anxiety disorders), which activate and maintain the cellular and molecular mechanisms of carcinogenesis, and open the way to the generalization of the cancer process (Figure 5). As it is seen in Figure 5, the psycho-emotional disorders (depressive and/or anxiety disorders) in cancer patients during CPES are accompanied by the disintegration of the major systems in the brain (Shumake and Gonzalez-Lima, 2003), in particular, persistent presence of over-active on sympathetic-adrenal-medullary and hypothalamic-pituitary-adrenal systems. In the state CPES, the central nervous system exerts downward tonic effect on the "target organs", accompanied by permanent disturbances of micro-circulation to form in the tissue where the cell's damage occurred (including DNA damage) by the products of oxidative-nitrosative stress (endogenous mutagens). Permanent tissue damage in the body simultaneously accompanied sanogenetic processes in order to repair damaged tissue with mandatory reciprocal inhibition of anti-tumor immunity for tissue healing. This is due to the fact that the restoration of normal tissue proliferating cells always express a number of tumor-associated antigens, so in case of high activity of anti-tumor immunity, repair processes would be difficult, since normal proliferating cells would be recognized as tumor-transformed.

Reparative focus of the immune system of cancer patients with psychogenic medical history is shown in a shift of balance T-helper-1/T-helper-2 lymphocyte subpopulations in the predominance of T-helper-2 lymphocyte subpopulations and the significant increase in the tissues of alternatively activated macrophages (M2 macrophages). These M2 macrophages are secrete IL-10, CCL17, CCL22, CCL18, IL-1RA, and IL-1R decoy. M2 macrophages are active workers of the host, promoting scavenging of debris, angiogenesis, remodeling, and repair of wounded/damaged tissues (Solinas et al., 2009). It is known that alternatively activated macrophages in tumor foci orient the immune response towards the activation of repair of processes in cancer centers, supports them in inflammation and angiogenesis, that is determine tumor growth and metastasis (Pollard, 2004). In tumor foci M2 macrophages take up to 50% of the tumor mass (Gordon and Martinez, 2010). It should be particularly noted that the induction of M2 macrophages is influenced by stress hormones – corticosteroids (Solinas et al., 2009). Thus, there is every reason to believe that the growth of the tumor and the generalization of cancer in the body of cancer patients with psychogenic medical history are determined by the phenomenon of reparative focus (direction) of their immune system. In general, the presented pathophysiological process in psychogenic carcinogenesis can be called "reparative trap" by the organism when the permanent tissue damage requires constant repair with appropriate suppression of antitumor immunity. Any additional damage in the body of a cancer patient with psychogenic carcinogenesis, including surgery, chemotherapy radiation therapy, enhances the phenomenon of a "reparative trap".

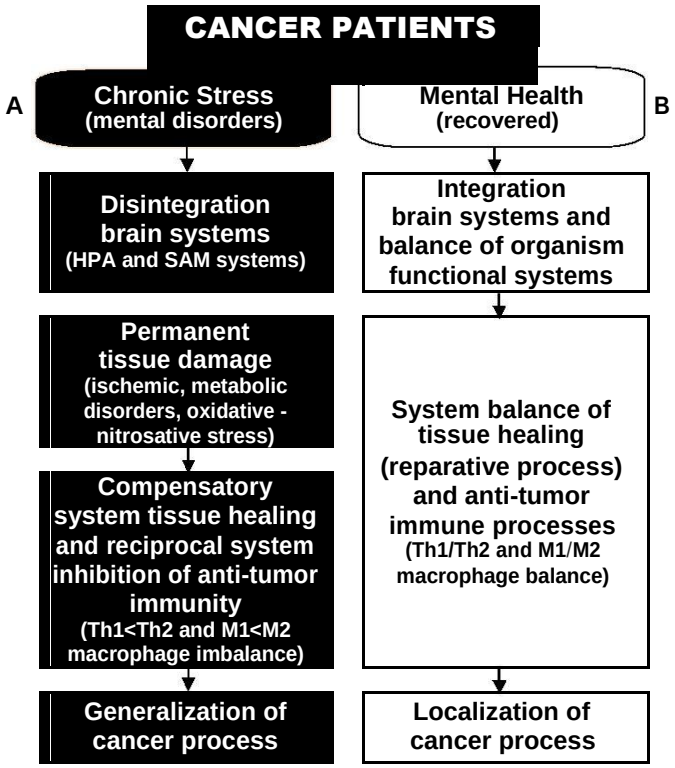

Figure 5. The role of chronic stress (mental disorders) in the generalization of the cancer process in patients with psychogenic medical history. (A) Psycho-emotional disorders (anxiety, depression) as a result of chronic stress in cancer patients with psychogenic medical history are accompanied by permanent damage to body tissues and compensatory systemic activation of sanogenic processes to repair damaged tissue. These system recovery processes are inevitably accompanied by systemic suppression of anti-tumor immunity, paving the way for the generalization of the cancer process. (B) Sustainable relief of psycho-emotional disorders in cancer patients restores the natural system activity of anti-tumor immunity and promotes the localization of the cancer process.

Our clinical observations suggest that cancer patients in general (and with psychogenic medical history in particular) no more and not longer than healthy people suffer colds, bacterial and fungal diseases. This points to the selective suppression of anti-tumor immunity, but not total compromising the immune system of cancer patients. Moreover, almost all cancer patients note a common or even accelerated healing of wounds, cuts, and scratches. These clinical data also reflect the reparative orientation of the immune system of cancer patients. In our view, the need to prove empirically the categorical prohibition of any cancer patient physiotherapy, enhancing tissue repair processes in the body, is connected with this phenomenon. The above mentioned fully applies to some psychotherapy. In particular, in cancer patients with not eliminated psycho-emotional disorders, the use of various relaxation techniques, as well as self-hypnosis or suggestion of warmth, improvement of blood supply and other trophically oriented therapeutic suggestion result in rapid progression of the cancer process. Moreover, cancer patients with non eliminated psycho-emotional disorders relaxed at the spa, in the tourist trip to relieve stress, relax, escape, recover, and often lead to progression of the cancer process shortly after returning home. Thus, the generalization of cancer in cancer patients with psychogenic medical history depends on the availability of non eliminated psycho-emotional disorders associated with compromising their anti-tumor immunity. In this regard, early detection and relief of psycho-emotional disorders in cancer patients with psychogenic medical history could prevent the transition of these patients in the category of advanced cancer patients. At the same time, advanced cancer patients with psychogenic medical history may have more favorable prognosis after they receive pathogenetically substantiated psycho-immunological rehabilitation.

Conclusion

The present study revealed that there is a special group of advanced cancer patients by the presence of their psychogenic medical history, comorbid psycho-emotional disorders, and suppressed specific anti-tumor activity of the immune system. Mentioned above characteristics we believe are the clinical criteria of the psychogenic (stressful) carcinogenesis. So, a co-morbid psycho-emotional disorders of this group of the advanced cancer patients have the major influence on the course and the outcome of the cancer disease. These patients need to hold a special psycho-immunological rehabilitation, consisting of two strictly sequential steps: elimination of psycho-emotional disorders, and activation of specific anti-tumor immunity. At the same time, the impossibility of sustained relief of psycho-emotional disorders in advanced cancer patients on the first stage of rehabilitation exclude further transition to immunological recovery phase and can be considered as an adverse prognostic factor with regard to the life of these patients. The results of this study are preliminary and require further clinical evidence on a larger contingent of patients with cancer and may be interested to various professionals involved in treating advanced cancer patients.

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Abbreviations

CPES, Chronic psycho-emotional stress; **DTH,** delayed

type hypersensitivity; **TAA,** tumor-associated antigens; **HSP,** hypnossugestive psychotherapy.

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