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Advanced Cancer Treatment – An Original Approach

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1. Introduction

Advanced cancer is a malignant disease that has spread to other places in the body and usually cannot be cured or controlled with treatment. The treatment and care of advanced cancer patients is focused on the management and relief of symptoms, improving the patient's comfort and quality of life. Such patients are given symptomatic treatment. At the same time the status of anti-tumour immunity is a key link in the carcinogenesis chain of advanced cancer. This means that anti-tumour immunity could be considered as a target for pathogenically justified immunotherapy. It is also known that the activity of anti-tumour immunity determines the survival of patients with cancer. It should be mentioned that an active development of immunotherapy had promised drastic changes in the management of cancer, as well as an increase in survival of patients living with cancer. However, that expectation has not yet been fulfilled. Clinical studies show that an initially compromised anti-tumour immunity of patients living with cancer cannot be surely recovered by means of immunotherapy. At the same time the use of immunotherapy in some cancer patients could be dangerous as well as useless due to the possibility of the stimulation of cancer development, for example through the induction of Treg cells [1]. At first sight an idea to administer pathogenically justified immunotherapy to patients with advanced cancer seems appropriate. However, it could be accepted if applied with immunotherapy for advanced cancer patients based on deterministic positions of cellular/molecular and/or genetic levels.

The systemic view in the whole body approach to treatment suggests mandatory consideration of the state of higher nervous activity (mental state), which provides a serious influence on the development and outcome of cancer disease. For instance, 'depression is worsening the potentially short lives of patients living with cancer' [2]. In this regard we assumed that some patients with advanced cancer suffer from psychogenically determined immunosuppression as an outcome of untreated psychoemotional disorders that have occurred before a diagnosis of cancer. In fact, those patients went through massive psychotraumatic events that accumu-

lated through the massive stress connected with a first diagnosis of cancer. We also assumed that the immunotherapy of advanced cancer patients with a psychogenic medical history should be preceded with an effective correction of psychoemotional disorders in order to avoid a psychogenic immunosuppressive influence. The objective of this work is the development and implementation of a psychoimmunological approach to the treatment of advanced cancer patients with a psychogenic medical history.

1.1. Theoretical justification for a psychoimmunological approach to the treatment of advanced cancer patients with a psychogenic medical history

Today there is no doubt that immune dysfunctions are the backbone of tumour pathogenesis. This immune dysfunction, along with destruction of the cellular genetic apparatus in the malignant cells, occurs in the form of the cell component of the immune system dysfunction along with the malfunction of cell control and cell differentiation mechanisms, immune tolerance, and inability to provide an effective immune response to a developing tumour [3, 4]. In this connection it was logical to use the wide range of immunotherapy methods in modern oncology. Despite being a new step in malignant tumour treatment it has not solved the problem of its effective treatment [5, 6].

At the same time, laboratory and clinical trials have shown linked and multi-functional interconnections between the two most important integrative systems of the human organism, which are the immune and the nervous systems [7-9], which formed the basis of the development of modern scientific trends of the psychoneuroimmunology and psychoimmunology of cancer [10]. The conclusions of the scientific research on the influence of chronic psychoemotional stress (CPES) to an organism of healthy and unhealthy individuals, including those with cancer, are most interesting from the practical point of view. Nowadays the somatic outcomes of CPES are well known: the CPES is able to damage the cell's DNA and inhibit DNA repair through the activation of endogenous mutagens, which are the reactive species of oxygen, nitrogen, etc. This leads to genome instability [11, 12]. CPES is always followed by immunosuppression, a decrease in the 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 the non-cropped areas of chronic inflammation [13-15]. All of these lead to a concentration of malignant cells in the body with an increase in their invasive potentiality [16]. CPES is linked with a high risk of development, progress and recurrence of malignant tumours, and the high mortality rate of cancer patients [17, 18]. The CPES also leads to hippocampal neuronal degeneration as well as amygdala atrophy [19], prolonged hyperactivity of the hypothalamo-pituitary-adrenocortical axis [20], and accelerated aging of the human body [21]. Therefore, the 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 a 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 to psychogenic influence and the suppression of anti-tumour 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 a psychogenic medical history. The confirmation of the dependency of anti-tumour immune activity to higher nervous activity is presented by the recently discovered phenomenon of the spontaneous

increase in anti-tumour activity of the immune system after the effective relief of psychoemotional disorders in cancer patients with a psychogenic medical history [22].

Thereby, advanced cancer patients with a psychogenic medical history require a special pathogenesis-based psychoimmunological cancer treatment in order to restore their mental condition, increase their quality of life, activate an anti-tumour immunity and to block the progression of cancer. The main content of psychoimmunological cancer treatment consists of compliance with a strict sequence of two stages of cancer treatment: psycho-correction and immunoactivation. The main objective of the first stage of cancer treatment (psycho-correction) is an effective and sustainable elimination of CPES effects that appear in different psychoemotional disorders such as anxiety, depression, etc. The main objective of the second stage of cancer treatment (stage of immunoactivation) is the activation of specific anti-tumour immunity.

2. Material and methods

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.

2.1. Characteristics of advanced cancer patients

The special psychoimmunological cancer treatment was offered to 17 patients with advanced cancer (13 women and four men). These patients, over seven years (2005-2012),were selected by us from the cancer patients using the following criteria: 1) the progression of the disease, despite the ongoing standard combination therapy of cancer provided, 2) the presence of distant metastases (stage IV of cancer), 3) the obvious massive psychotrauma that occurred in the lives of patients before being diagnosed with cancer (psychogenic medical history), and 4) informed consent of cancer patients for carrying out cancer treatment. A special clinical case was associated with patient № 9 (Table 1), who strictly refused to take a standard combination therapy for cancer, but expressed the strong desire to receive psychological and psychotherapeutic aid. Individual characteristics of cancer patients are presented in Table 1.

| Patient № | Age | Sex | Cancer types | Primary tumour 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 |

| Patient № | Age | Sex | Cancer types | Primary tumour localization | Metastasis localization | Stage | Comorbidities | Treatment |
|-----------|-----|-----|--------------------------|-----------------------------|--------------------------------------------------|-------|-----------------------------------------------------|---------------------------|
| 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 & feet | IV | Chronic cholecystitis | SUR, CHT |
| 7 | 38 | F | Melanoma | Skin of temporal region | Retroperitoneum | IV | - | SUR, CHT |
| 8 | 53 | M | Melanoma | Back skin | Subcutaneous hands & feet | IV | Stomach ulcer | SUR, CHT |
| 9 | 55 | F | Melanoma | Neck skin | Supraclavicular & axillary lymph nodes | IV | - | Refuse standard treatment |
| 10 | 76 | F | Kidney cancer | Right kidney | Both lungs, mediastinal & 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& pancreas cancer | Stomach& pancreas | Paraortic 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

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

2.2. Psychogenic medical history investigation

Psychogenic medical histories were taken for each patient in the clinical trial (anamnesis morbi) during the first visit, and these histories included the presence of massive psychotraumatic events (death of close person, divorce, etc.) with the development of helplessness and despair.

2.3. The mental status examination of advanced cancer patients

The mental status examination of cancer patients was conducted by the psychiatrist with supplemental usage of the following psychometric test systems (e.g., 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 [23]. The mental status examination was administered in the following stages of research: 'before' – before psycho-correction; 'after' – after hypnotherapy session; and 'one month later' –hypnotherapy sessions one month later.

2.4. The pharmacotherapy of psychoemotional disorders

The pharmacotherapy of mental disorders in advanced cancer patients was conducted immediately after diagnosis. Antidepressants (tianeptine, venlafaxin), anxiolytics (afobazolum, microdoses of diazepam) and their combination were used. The psychotropic drugs were prescribed for a period of three to six months to enhance and prolong the therapeutic effect of hypnosuggestive psychotherapy (HSP).

2.5. Method of hypnosuggestive psychotherapy

The method of hypnosuggestive psychotherapy is based on strict successive, interconnected, figurative, pathogenically substantiated suggestive influences in hypnotic states. This method has previously been described in detail [24]. It includes: 1) Establishment of hypno-rapport between patient and physician; 2) Hypnotic de-actualization of psychotraumatic emotions and experience including the fact of cancer diagnosis; 3) Hypnotic lockout of dreams connected with known stress situations which are regularly reproduced in sleep with the corresponding psycho-vegetative reactions – this 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 the known phenomenon of hypnotic hypermnesia (increased memory under hypnosis), generally used for the restoration of psychogenic abnormalities of memory. However, it is possible to restore the memory of the heartbeat, respiratory rate, glycaemic rate, enzyme reaction activity, stereotype of digestive system functions, etc. from a specific time in the past. The patient recollects the concrete day (date, month, year) from the past – the 'model standard' of his health when there was no tumour and he felt well, mentally and physically. In a hypnotic state suggestions were conducted using the images required to retrieve the 'records' that are well known to the body as 'health standard' from the memory of cancer

patients. It should be noted that in this key session HSP hypnotic suggestions related to the activation of a great desire and the need for further self-realization in their lives were conducted. In fact, these suggestions were aimed at restoring of life purpose dominant loss [25]; 5-6). The last HSP sessions focused on patients' education in self-hypnosis (autohypnosis) under suggestive influence. The patients were then given detailed instructions to use self-hypnosis for the prolongation of the medicinal effect, as well as keeping the psychic and vital tone of cancer patients. The duration of the individual course of the HSP was 14-16 days.

2.6. Anti-cancer diagnostic skin test for evaluation of specific anti-tumour activity of the immune system (non-stimulated native activity) in advanced cancer patients

The anti-tumour activity of the immune system was assessed by a skin test of the delayed type hypersensitivity (DTH) reaction on tumour-associated antigens (TAA), which were used as a lysed human melanoma cell line BRO [26] of 25,000 cells in a test (see Figure 1). Human melanoma cell line BRO was obtained at the Institute of Cytology of the Russian Academy of the Sciences (St. Petersburg, Russia). We investigated the DTH skin reaction after the intradermal administration on the forearm at 9, 12 and 24 hours, to identify the peak responses. The peak response in most cases (the diameter of redness in mm) was observed after 12 hours. Selection of the human melanoma cell line BRO was determined by the need to use in one test the maximum range of TAA, in order to assess the anti-tumour activity of the immune systems of patients with different cancers. As shown above, there exist all kinds of TAA characteristics of solid tumours on the melanoma cells [27].

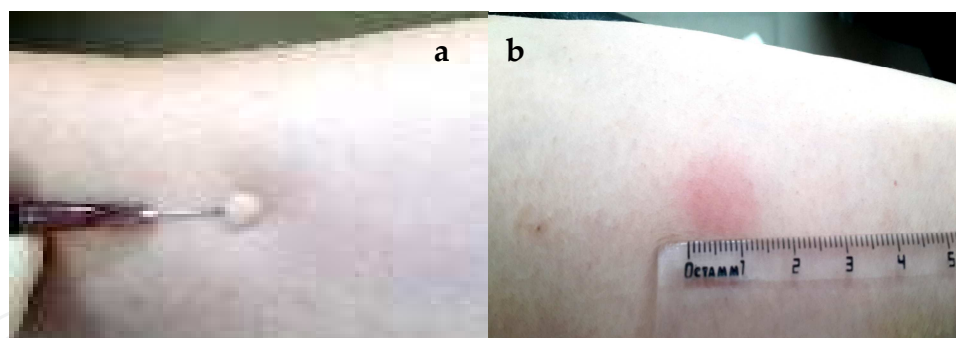


Figure 1. Anti-cancer diagnostic skin test: evaluation of specific anti-tumour activity of the immune system in advanced cancer patients (Patient № 11 after psycho-correction). (a) Intradermal introduction of tumour-associated antigens: lysed cells of human melanoma line BRO 25×10^3 per dose (50 μ L); (b) Evaluation of DTH skin reaction on TAA (12 hours later): 0-5 mm – low activity, 5-10 mm – average activity, >10 mm – high activity.

The selection of the minimal quantity of TAA for the anti-cancer diagnostic DTH skin test (according to our preliminary studies) was used in order to obtain a physiological specific anti-tumour immunological response (non-stimulated native DTH skin reaction on TAA) as well as to exclude the possibility of the vaccine's effect on the diagnostic test itself. In comparison with our colleagues, who used the DTH skin reaction on the TAA of human melanoma cell lines in a study of the clinical efficacy of the anti-tumour polyvalent vaccine 'CancerVax' (USA) (developed from three allogeneic human melanoma cell lines) [28], we used a diagnostic dose

that was nearly 100 times smaller (2.5×10^4 cells vs. 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 eight to 12 hours after ingestion of antigen, and in most cases the reaction reaches a peak after 48-72 hours [29].

In our case the peak responses, due to the absence of prior immunization of cancer patients and the largest contribution of cellular reactions in the DTH skin test, were achieved early (within 12 hours) [30]. An evaluation of a specific anti-tumour activity of the immune system in advanced cancer patients was conducted through the research phases: 'before' – before psycho-correction, 'after' – after completing a course of hypnotherapy and 'one month later' – after one month following the completion of the course of hypnotherapy.

2.7. Preparation of tumour-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 foetal calf serum, L-glutamine (2 mmol/ml), 25 mmol HEPES buffer, and 25 µg/ml gentamicin at 37°C in 5% CO₂ 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 (eight times) freezing and stored at -80°C until use. As a diagnostic test 2.5×10^4 lysed cells line BRO in 50 microliters were used.

2.8. Preparation of tumour-associated antigens for epicutaneous activation of specific anti-tumour immunity

The lysed cells of the human melanoma cell line BRO were used as the TAA for epicutaneous activation of specific anti-tumour immunity. The human melanoma cell line BRO was maintained in RPMI 1640 supplemented with 10% heat-inactivated foetal calf serum, L-glutamine (2 mmol/ml), 25 mmol HEPES buffer, and 25 µg/ml gentamicin at 37°C in 5% CO₂ 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 freezing (eight times) and stored at -80°C until use. The one epicutaneous activation of specific anti-tumour immunity was performed with the use of a 2.5×10^6 lysed cells line BRO in 0.5 ml.

2.9. Preparation of tumour-associated antigens for extracorporeal activation of specific anti-tumour immunity

Lysed placental domestic pig cells were used as the TAA for extracorporeal activation of specific anti-tumour 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 a concentration of 50×10^6 placental cells in 1.0 ml. Cells were lysed by repeated freezing (eight times) and stored at -80°C until use.

2.10. Extracorporeal activation of specific anti-tumour immunity

A peripheral blood mononuclear cell (PBMC), separated from 25 ml of heparinized cancer patient blood was diluted in RPMI 1640 and supplemented with 20% autologous plasma, L-glutamine (2 mmol/ml), 25 mmol HEPES buffer, and 25 µg/ml gentamicin. PBMC in concentration 4×10^6 cells/ml was placed in a cell culture dish in the proportion $1-2 \times 10^6$ cells/sm². The lysed domestic pig placental cells were used as the antigen at a proportion of 1/6 (lysed cells of pig placenta/PBMC). This proportion was found to be optimal in previous research. Further PBMC with added antigen was placed into a CO₂ incubator and incubated at 37°C in 5% CO₂ humidified air. The incubation time was six to eight hours for antigen processing by monocytes of PBMC. The PBMC was collected after completion of incubation by rubber policeman and was triplewashed in the phosphate buffer solution with the addition of 5% autologous plasma of the cancer patient. The washed incubated PBMC was diluted in 2 ml of autologous plasma from the cancer patient and shared between two 1 ml syringes. Incubated PBMC was administered subcutaneously in the subscapular fossa area and in the area of the lower abdomen laterally from the umbilicus (palm width sinistral or dextral). A total of three procedures were provided, the second after two weeks and the third after one month from the first procedure.

2.11. Epicutaneous (scarification) activation of specific anti-tumour immunity

The superficial line scarifications were applied after skin disinfection on the area of 4 cm² with a gap in between lines of 2-3 mm wide by blood lancet (scarificator) (see Figure 2). The damaged area was covered by sterile patch underneath which a solution with TAA (2.5×10^6 lysed cells line BRO in 0.5 ml) was administered by syringe. The subclavicular and subscapular areas were used for the epicutaneous application of TAA. The exposition of patch was left for three days. Four sessions of epicutaneous activation of specific anti-tumour immunity were administered with a 14-day break and three sessions were provided with a 30-day break.

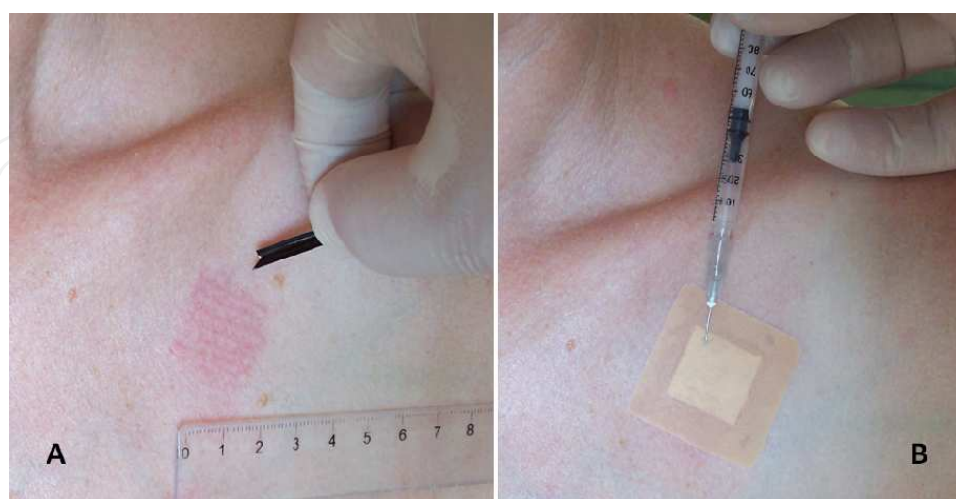


Figure 2. Epicutaneous (scarification) activation of specific anti-tumour immunity. (A) The superficial line scarifications plotted after skin disinfection by blood lancet (scarificator); (B) Patch (with viscose bandage) is superimposed on the network of surface scarification and impregnation of bandage patch by solution of tumour-associated antigens.

2.12. Statistical analysis

The statistical data processing was performed 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 psychometric (SCL-90) and immunological (DTH skin reaction on TAA) parameters was carried out using Pearson's correlation test.

3. Results

3.1. Mental disorders in advanced cancer patients with psychogenic medical history

Clinical studies of 17 advanced cancer patients with a psychogenic medical history showed that 100% had a variety of psychoemotional comorbidity disorders, predominantly anxiety and depression spectrum disorders. The disorders distribution was based on the International Classification of Diseases (ICD-10): generalized 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 advanced cancer patients in general have been confirmed by the data of psychometry (Table 2, the indicators 'before').

3.2. Psycho-correction stage is the first stage of psychoimmunological advanced cancer treatment

The clinical benefits after completion of HSP have been noted in all advanced cancer patients. This was confirmed by the results of psychometry and comparative analysis, which showed significant improvement in almost all of the parameters studied (Table 2). Along with a significant improvement in the mental state of cancer patients a spontaneous increase in the specific anti-tumour activity of the immune system was 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 stage of psychoimmunological cancer treatment which is the stage of immunoactivation. In this regard, the studied parameters at the 'one month later' stage 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).

However, a careful study of the indicators at 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

| Indicators | Normative values [†] | Comparative analysis 'before-after' and 'after-one month later' | | | | |
|------------------------------|-------------------------------|-----------------------------------------------------------------|---------------|---------------|--------|----------|
| | | Before (B) | After (A) | 1 month later | P | P |
| | | Mean ± s.e.m. | Mean ± s.e.m. | Mean ± s.e.m. | B-A | 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 ± s.e.m. – means and standard errors means; *P>0.05; † - Normative values for healthy people (Tarabrina N.V., 2001)

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

DTH skin reaction was less than 5 mm in one group of patients, and was greater than 5 mm in the other group. It was found that cancer patients in these groups differed substantially in almost all psychometric parameters. The group of patients with a DTH skin reaction of less than 5 mm (11 of 17 patients) was characterized by the deterioration of psychometric indicators, which allowed us to identify this group of patients as a group with an unstable effect of correction of psychoemotional disorders (patient № 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 the conduction of self-hypnosis sessions. Another group of patients whose DTH skin reaction was more than 5 mm (six patients) differed by maintenance of the previously achieved positive effects of psycho-correction with appropriate psychometric characteristics. The last group was identified by us as a group of patients with a stable effect of psycho-correction (patients number 2, 9, 10, 11, 14, 16). The close relationship of specific anti-tumour 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 psychometric parameters of SCL-90 at all stages of observation (Table 4).

| Indicators | Normative values [†] | Unstable effect (n=11) | Stable effect (n=6) | P |
|------------------------------|-------------------------------|---------------------------|------------------------|--------|
| | | Mean ± s.e.m. | Mean ± s.e.m. | |
| 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 ± s.e.m. – means and standard errors means; *P>0.05; † - Normative values for healthy people (Tarabrina N.V., 2001)

Table 3. A comparative analysis of the studied parameters in cancer patients with unstable and stable effects of correction of psychoemotional disorders

| Indicators | DTH skin reaction on TAA, mm | | | | | |
|---------------------------|------------------------------|---|-------|-------|-----------------|--------|
| | Before | | After | | One 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 |

* P>0.05

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

The dynamics of the relationship showed that the medical and psychotherapeutic effect on the higher nervous activity of the cancer patients was accompanied by a cumulative increase in the significant negative correlations between the specific anti-tumour activity of the immune system and the mental wellbeing of cancer patients. The greatest number of correlations was observed month after the completion of HSP. Cancer patients with a sustained effect of psycho-correction (patient № 2, 10, 11, 14, 16) were proposed for a second stage of psychoimmunological cancer treatment (stage of immunoactivation), except for patient № 9.

3.3. Stage of immunoactivation: the second stage of psychoimmunological advanced cancer treatment

The stage of immunoactivation lasted for five months and, along with the procedures of activation of specific anti-tumour immunity, advanced cancer patients took psychotropic medications and performed self-hypnosis sessions. Each procedure of epicutaneous activation of specific anti-tumour 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 tumour formation (including previously undiagnosed) as well as pain in the regional lymph nodes on the third day, sometimes an increased body temperature up to 37°C, and deterioration of health in the form of weakness, lethargy, and sleepiness. In order to relieve these reactions, patients received Nise (nimesulide) tablets 100 mg, twice per day for five to seven days. Procedures of extracorporeal activation of specific anti-tumour immunity were also accompanied by systemic reactions, but were 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.

3.4. Catamnesis

The advanced cancer patients experiencing unstable clinical effects of the correction of the psychoemotional disorders (patient № 1, 3, 4, 5, 6, 7, 8, 12, 13, 15, 17) died within two to five months of the psycho-correction stage being over, except patient № 5 who died after one year. These advanced cancer patients are likely to have had more pronounced somatopsychic disorders that were not consistently removed with psycho-correction techniques and failed to influence anti-tumour immunity. Among the advanced cancer patients that were subjected to psychoimmunological cancer treatment (patient № 2, 10, 11, 14, 16) the following results were observed.

Patient № 2 is alive (five years catamnesis). The signs of haemangioma were revealed in the place of former liver metastasis (Ultrasound data) in one year following the psychoimmunological cancer treatment.

Patient № 10 is alive, and catamnesis was two years without substantial negative dynamics. Multiple foci of fibrosis and calcification were discovered by computed tomography.

Patient № 11 is alive, and catamnesis was 6.8 years after psychoimmunological cancer treatment had finished. A very interesting fact was revealed during the research. After massive stress (she found out about her daughter's drug addiction), a quick development of the cancer

disease was observed and within seven days the size of the metastasis in the only kidney increased from 38×23 mm to 41×32 mm. After the effective relief of psychoemotional disorders, metastasis regression to 12×11 mm was observed.

Patient № 14 is alive, and catamnesis was 1.1 years. Multiple foci of osteosclerosis without negative dynamics were observed (on computed tomography).

Patient № 16 is alive, catamnesis was four years. Negative dynamics were not observed, pneumosclerosis foci and extensive fibrotic process were observed in the mediastinum (on computed tomography).

3.4.1. Clinical case (patient № 9)

We have observed the unique clinical case of the cancer patient with malignant melanoma, who refused to receive mutilating surgery and chemotherapy but approached us for psychological help.

Patient № 9, 55 years old, an accountant. In autumn 2004, melanoma localized on the neck on the left side was histologically verified. The patient turned to us on 20 January 2005. It was examined that the patient had a 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 (see Figure 3).

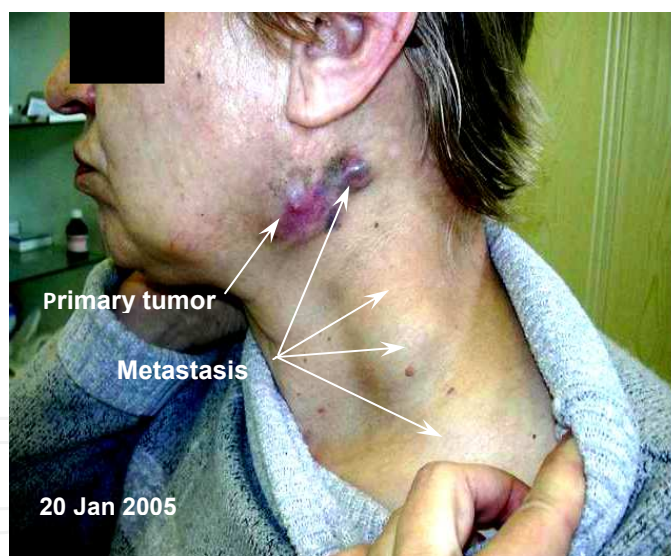


Figure 3. Localization of malignant neck melanoma, patient № 9.

Ultrasound examination of the primary tumour revealed the depth of tumour invasion in the tissues of the neck to be 25 mm.

After examination the patient was diagnosed with a psychogenic medical history (she lives with a disabled husband, who is an alcoholic), mixed anxiety and depressive reaction (F43.22) and the lack of inhibition of specific anti-tumour activity of the immune system, defined by the absence of DTH skin reaction on TAA. We observed that patients with a similar localization

of melanoma die within four to six months due to profuse bleeding from the tumour foci and frequent metastasis to the brain. From 21 January to 4 February 2005 the patient underwent a course of hypnotherapy consisting of four treatment sessions and two sessions of self-hypnosis training. After treating the patient with HSP (5 February 2005), along with an improvement in general state of health and relief of anxiety and depressive disorders, positive changes were seen in a number of objective indicators.

Thus, DTH skin reaction on TAA increased from 15 mm (before HSP) to 40 mm (after HSP) and maintained for two days, the absolute number of peripheral blood lymphocytes increased three times: from 709 to 1 mm³ (before HSP) to 2244 in 1 mm³ (after HSP). In addition there was a change of the vegetative (autonomic) nervous system, which was assessed by heart rate variability (HRV) [31]. HRV is the assessment of individual differences in emotional reactions, particularly in relation to social processes and mental health [32]. The total energy spectrum analysis (TP of HRV) increased 20-fold: from 213 ms² (before HSP) to 4260 ms² (after HSP). In addition there was a reduction in the ratio of LF/HF (normalized units) five-fold: from 2.76 (before HSP) to 0.53 (after HSP), indicating a change of state of sympathicotonia to the state of parasympathicotonia and this is a confirmation of the clinical fact of depression relief [33]. After the completion of HSP the patient conducted daily self-hypnosis sessions in accordance with our proposed programme, the content of which was aimed at forming a dense impermeable capsule around the tumour foci, which like a 'plaster cocoon walls up, squeezes and strangles tumour foci'. After several self-hypnosis daily sessions lasting one hour each of the pronounced swellings of the left side of the neck and supraclavicular area with transition to the chest were observed (see Figure 4); body temperature rose up to 38°C; and itching of the tumour foci appeared.

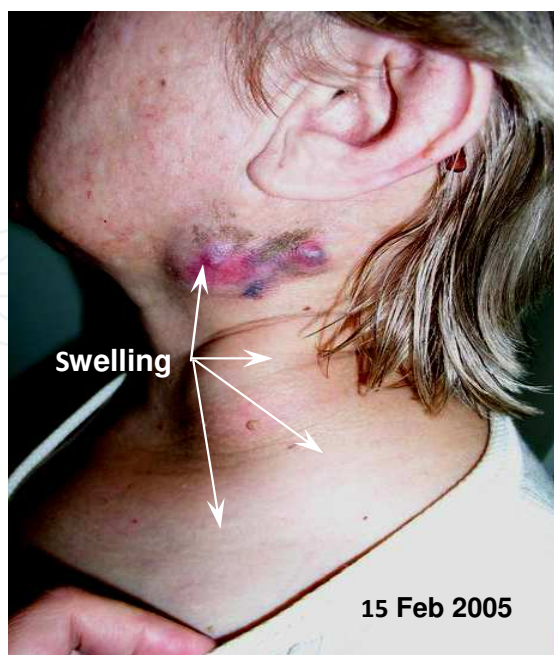


Figure 4. Pronounced swelling of the neck tissues after organic-oriented self-hypnosis sessions

The patient reported that ‘stifling of the tumour’ started. Within eight 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 an organic-oriented suggestive programme ‘stifling of tumour foci’. Nine months after the beginning of organic-oriented therapeutic autosuggestion (03 November 2005), the patient underwent ultrasound examination of the tumour foci.

The results showed regression of metastatic lymph nodes in the neck, in the supraclavicular and axillary regions. A fibrous capsule (see Figure 5) formed deep in the tissues of the neck throughout the borders of the tumour invasion of the primary tumour focus, which actually corresponds to the content of curative autosuggestion.

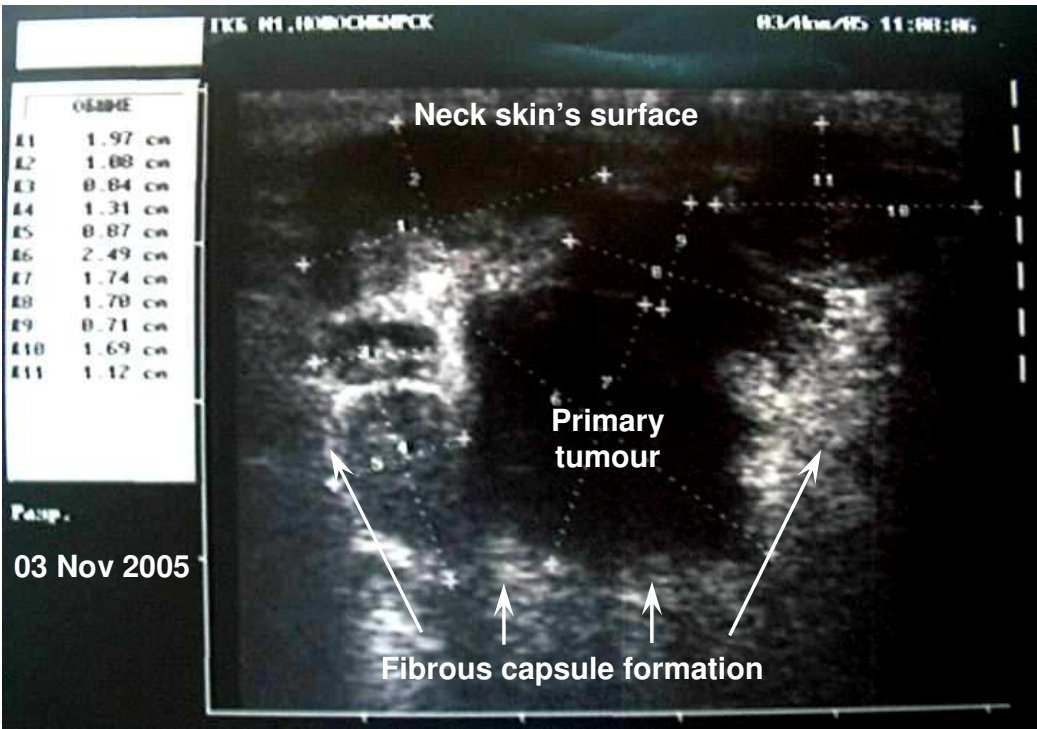


Figure 5. Fibrous capsule around the primary tumour in the depth of the neck tissues after self-hypnosis sessions (ultrasound data).

Further observation showed that endophytic growth of the primary tumour focus changed to exophytic growth (tumour 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 (see Figure 6).

Hereinafter, a slow progression of the cancer process with a gradual increase of phenomena cachexia was observed. The patient died on 14 April 2008. Despite the expected death, it can be stated that the cancer patient had been able to live an active life for three years without surgery on the neck melanoma.



Figure 6. Exophytic growth of melanoma with metastasis regression in the lymph nodes of the neck and supraclavicular area against self-hypnosis treatment sessions

4. Features of our approach

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

The study of psychogenic medical history showed that all patients were in a state of obvious emotional stress before cancer diagnosis (on average for one and a half years), which was caused by psychotraumatic events such as death of a close person, divorce, frequent family conflicts, change of residence, work and the presence of a disabled person in family. This long-term emotional tension was accompanied by the formation of the feeling of helplessness, hopelessness, and despair. We can assert that these future cancer patients, long before the diagnosis of cancer, already had psychogenically caused psychoemotional and psychosomatic disorders. The diagnosis of cancer itself is an additional massive and inexhaustible psycho-trauma, causing emotionally paralyzing fear, or so-called 'Damocles syndrome' [34].

Cancer patients with a psychogenic medical history are those with a double massive psycho-trauma. Advanced cancer patients with a psychogenic medical history undoubtedly form somatopsychic disorders along with cancer progression, so these patients were observed with a combination of psychosomatic and somatopsychic disorders that were clinically difficult to differentiate. The main feature of psychiatric disorders that we have found in cancer patients with a psychogenic medical history is that, despite the urgency of the massive psychotrauma and other conditions for the development of neuroses (known as neurotic 'Jaspers' triad'), cancer patients show a condition that is opposite to neurosis and can be defined as a state of

‘deneurotization’. This phenomenon is clinically manifested by blurry, non-deployed with denial to accept, so cancer patients themselves do not consider their mental condition to be sick but quite natural and 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 an inconsistency of psychometric assessments to clinical studies. In other words, psychoemotional disorders in a clinical study are obvious, but psychometric parameters are within the normal limits, and vice versa. 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 through a self-reported screening instrument without clinical examination does not provide a fair view of psychopathology in cancer patients.

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

For the fastest and most effective correction of psychoemotional disorders in advanced cancer patients, a combination approach was selected that involves the simultaneous use of psychotropic drugs and hypnotherapy. This approach was driven by the severity of the 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 its high efficiency and velocity of clinical benefit achievement, including in oncology [35]. Thus, comparative analysis has shown that after 600 sessions of psychoanalysis 38% of patients reported feeling better, after 22 sessions of behavioural therapy 72% of patients reported a positive result, and after six sessions of hypnotherapy 93% of patients referred to the desired effect [36].

Our 26 years of clinical experience confirm the major clinical capabilities of hypnosuggestive psychotherapy in the correction of mental and psychosomatic disorders. In particular, we first discovered the phenomenon of psychogenic mobilization of CD34+CD38- stem cells [37] and an increase in telomere length in peripheral blood mononuclear cells in cancer patients during hypnotherapy [38]. Later, this phenomenon was to some extent confirmed by other researchers using psychosocial telephone counselling intervention [39]. It should be noted that because of the state of hyper-suggestiveness of advanced cancer patients there is a risk of the formation of hypnotic dependence (hypnomania), so the number of HSP sessions was limited to six sessions of hypnotherapy.

4.3. DTH skin reaction on TAA as a biomarker of removing mental disorders in cancer patients

It can be assumed that the spontaneous increase in the specific anti-tumour activity of the immune system, as determined by DTH skin reaction on TAA, reflects a relief of the psychogenic immunosuppressive effects of higher nervous activity on the anti-tumour activity of the immune systems of advanced cancer patients. In fact, the DTH skin reaction appeared to be a kind of biological marker of the presence or absence of psychoemotional disorders in advanced

cancer patients with a psychogenic medical history. It can be assumed that the initial absence of correlation between the DTH skin reaction and psychometric parameters was likely caused by the disintegration processes in the organism of advanced cancer patients inter alia by the 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 the gradual recovery of damaged linkages between the nervous and immune systems of the body. These data indicate a significant effect of higher nervous action on the anti-tumour activity of the immune system of advanced cancer patients with a psychogenic medical history.

4.4. Features of immunoactivation

The main task of the immunoactivation stage was to stimulate the specific anti-tumour immunity of advanced cancer patients by immunological methods after a spontaneous increase of their immune system's anti-tumour activity resulting from the sustained relief from psychoemotional disorders. Presumably, the effective activation of the specific anti-tumour immunity had to have a positive impact on the course of the cancer disease. We have therefore developed a method of epicutaneous (scarification) activation of specific anti-tumour immunity and an extracorporeal activation method using a small amount of peripheral blood. Both methods in preliminary studies have shown high effectiveness and safety in clinical practice (unpublished data). It should be noted in particular that the very low dose of TAA administered per epicutaneous led to systemic reactions in the whole body. It can be assumed that such a clinical effect was due to the specific systemic immune responses associated with the capture of TAA by antigen-presenting epidermal Langerhans cells and the migration of these cells to regional lymph nodes and antigen-presenting TAA. The latest data indicate a greater potential of CD8⁺ cell activation by Langerhans cells [40]. 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 tumour foci. We observed the systemic clinical manifestations of these processes on the third day.

4.5. Mind and tumour encapsulation

Scientific and clinical evidence shows that cancer has always been primarily a local tissue process. Ideally the focus of the tumour should be immunogenic, and is supposed to be recognized by the immune system as allogeneic, and thus localized (delimited) and destroyed by the cell-effectors of specific anti-tumour immunity. In this case, the encapsulation process is a universal natural mechanism of localization of anything allogeneic in the body. This fully applies to the localization of malignant tumour formation. A fibrous capsule of a different density around the tumour foci has always been observed in experimental animals. It is interesting that the structure of the extracellular macromolecule matrix in capsules around the malignant and benign tumours does not differ [41]. In clinical practice, we often see a favourable course of cancer regardless of the tissue localization when a dense fibrous capsule is formed around the tumour foci. In fact, the formation of a fibrous capsule is associated with low levels of cancer recurrence, and a capsule can serve as a mechanical and chemical barrier to metastasis [42]. Other authors in clinical practice found that the encapsulation of the tumour was an

important favourable prognostic factor for survival without signs of cancer disease [43]. In this regard, we have developed an organic-oriented treatment programme for self-hypnosis, which could presumably have a decreased trophic effect on tumour tissue and contribute to the induction of tumour encapsulation. The examined clinical case confirms what is known about the significant impact of the brain and higher nervous activity on cancer [44]. Furthermore, this case presents new data on the possible nutritional (trophic) effects on tumour tissue and on suppressing the cancer process by deliberate action on higher nervous activity in cancer patients.

4.6. ‘Cancer reparative trap’: the pathophysiology of cancer in cancer patients with a psychogenic medical history

Analysis of the literature led to the conclusion of the existence of the physiological inhibition of specific anti-tumour immunity in the reparative process (see Figure 7).

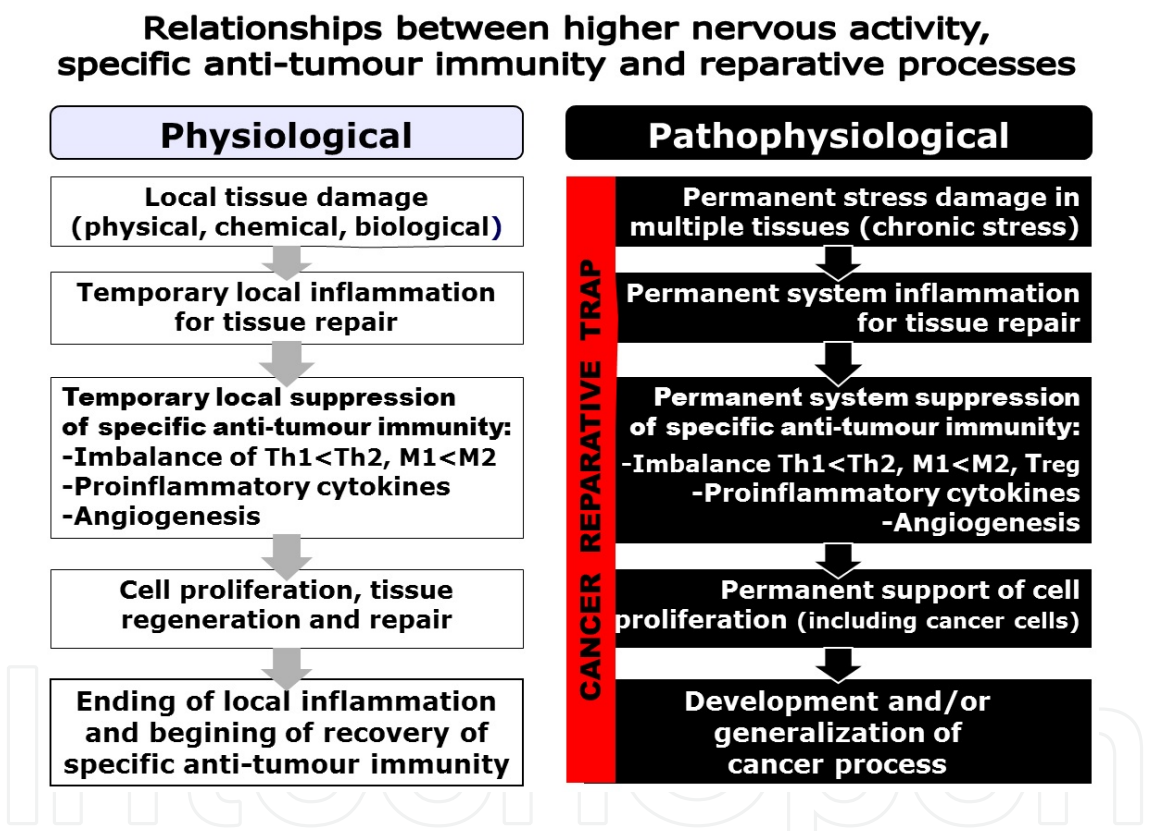


Figure 7. The pathophysiology of cancer in cancer patients with psychogenic medical history.

This local inhibition is observed in local tissue damage as a result of chemical, physical or biological exposure. For the successful healing of tissue damage, local inflammation with known cell, cytokine and vascular reactions develops in the focus. The key factor for successful tissue repair is temporary local suppression of specific anti-tumour immunity in order to avoid the elimination of proliferating cells in the damaged tissue. After completing the repair process, the local inflammation is reduced and the activity of anti-tumour immunity is restored. This natural physiological mechanism of tissue repair may become pathophysiological, i.e., as a result of chronic psychoemotional stress in the body, many foci of the stress microdamages of

different tissues, which cause the formation of numerous foci of inflammation, are constantly formed. Because of the large number of inflammatory lesions in the body, there is a constant imbalance of immune reactions in the direction of maintaining reparative processes. This imbalance is accompanied by the constant systemic oppression of specific anti-tumour immunity. Under these conditions cancer tumour cells are able to grow, while the existing tumour in the body creates the possibility of the spreading of cancer. It can be stated that, in cancer patients with a psychogenic medical history, psyche is the leading factor in the development and metastasizing of cancer.

The leading role of the central nervous system in the generalization of cancer has also been shown in an animal model: in the paper of Erica Sloan and colleagues from Monash University, Melbourne, Australia, a 30-fold increase in metastasis to distant tissues from primary tumours was demonstrated in stressed mice [45]. In general, the presented cancer pathophysiological process in cancer patients with a psychogenic medical history can be called a '*cancer reparative trap*' when permanent tissue damage requires constant repair with the appropriate suppression of anti-tumour immunity.

It should be noted in particular that permanent tissue damage is also observed to be influenced by the organism's chemical, physical and biological carcinogens. Thereby, cancer is a disease of an organism that is located in the reparative trap. Any additional damage in the body of an advanced cancer patient with a psychogenic medical history, including surgery, chemotherapy, or radiation therapy, enhances the phenomenon of a '*cancer reparative trap*'. The elimination of mental disorders in cancer patients with psychogenic carcinogenesis leads the patient's body out of a '*cancer reparative trap*' by creating the conditions for managing the cancer process and increasing the efficiency of standard cancer therapy.

4.7. The role of the mind in the generalization of the cancer process

The cellular and molecular factors and mechanisms of cancer's generalization have been presented in detail; the determinants of invasiveness and the invasion-metastasis cascade have been studied [46]; and the tumour-induced immunosuppressive network has been shown [47]. There is also evidence that biobehavioural risk factors such as social adversity, depression, and stress are involved in cancer progression [48, 49]. As mentioned above, 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 kind of fertilizer that feeds breast cancer progression, significantly accelerating the spread of the disease in animal models [45, 50]. It can be argued with a certain degree of confidence that chronic stress is also a kind of fuel for the 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 a 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 (see Figure 8).

As can be seen in Figure 8, psychoemotional disorders (depressive and/or anxiety disorders) in cancer patients during CPES are accompanied by the disintegration of the major systems in the brain [51], in particular the persistent presence of the sympathetic-adrenal-medullary and

hypothalamic-pituitary-adrenal systems prevalence (fight or flight response). In the CPES state 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-tumour immunity for tissue healing. This is due to the fact that, with the restoration of normal tissue, proliferating cells always express a number of tumour-associated antigens; in case of the high activity of anti-tumour immunity repair processes would be difficult, since normal proliferating cells would be recognized as tumour-transformed.

The reparative focus of the immune systems of cancer patients with a 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 a significant increase in the tissues of alternatively activated macrophages (M2 macrophages). These M2 macrophages secrete IL-10, CCL17, CCL22, CCL18, IL-1RA, and IL-1R decoy. M2 macrophages are active workers of the host, promoting the scavenging of debris, angiogenesis, remodelling, and repair of wounded/damaged tissues [52].

It is known that alternatively activated macrophages in tumour foci orient the immune response towards the activation of repair processes in cancer centres, supporting them in inflammation and angiogenesis, i.e., determining tumour growth and metastasis [53]. In tumour foci M2 macrophages take up to 50% of the tumour mass [54]. It should be particularly noted that the induction of M2 macrophages is influenced by stress hormones – corticosteroids [52]. Thus, there is every reason to believe that the growth of the tumour and the generalization of cancer in the body of patients with a psychogenic medical history are determined by the phenomenon of the reparative focus (direction) of their immune system.

Our clinical observations suggest that cancer patients in general (and with a psychogenic medical history in particular) suffer colds, bacterial and fungal diseases no more and for no longer than healthy people. This points to the selective suppression of anti-tumour immunity but not completely 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 abovementioned fully applies to some psychotherapy. In particular, for cancer patients with psychoemotional disorders that have not been eliminated, the use of various relaxation techniques as well as self-hypnosis a hypnotic inductions of warmth, improvement of blood supply and other trophically-oriented hypnotic inductions, result in the rapid progression of the cancer process. Moreover, cancer patients with psychoemotional disorders that have not been eliminated who relax at the spa, make tourist trips and so on to relieve stress, relax, escape, and recover, often experience progression of the cancer process shortly after returning home.

Thus, the generalization of cancer in cancer patients with a psychogenic medical history depends on the availability of psychoemotional disorders that have not been eliminated

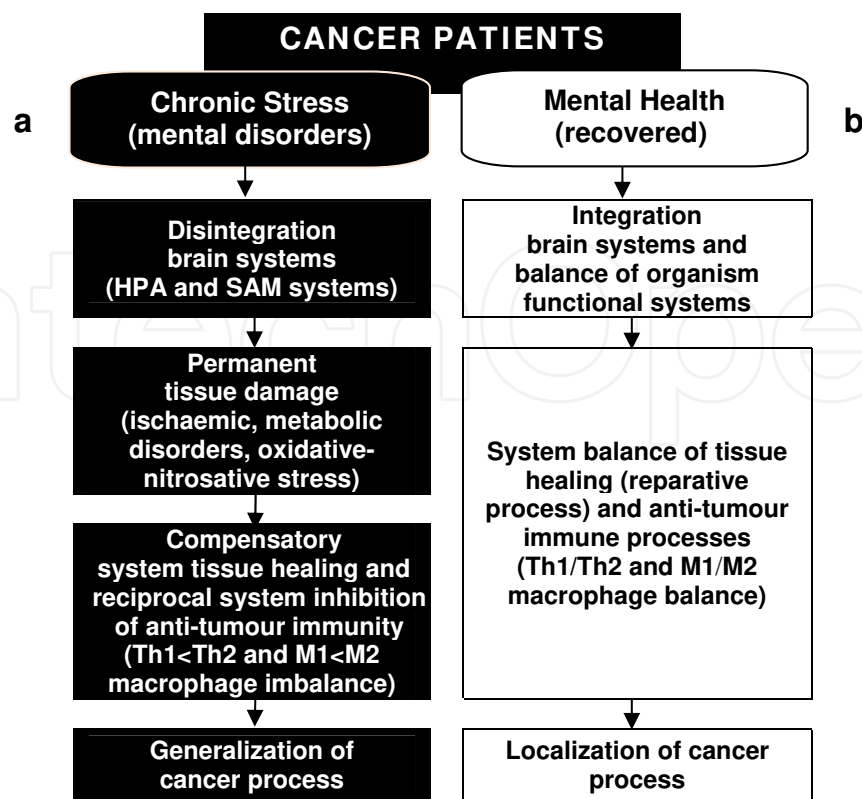


Figure 8. The role of chronic stress (mental disorders) in the generalization of the cancer process in patients with psychogenic medical history. (a) Psychoemotional disorders (anxiety, depression) as a result of chronic stress in cancer patients with psychogenic medical history are accompanied by permanent damage to body tissues and compensatory systemic activation of sanogenetic processes to repair damaged tissue. These system recovery processes are inevitably accompanied by systemic suppression of anti-tumour immunity, paving the way for the generalization of the cancer process; (b) Sustainable relief of psychoemotional disorders in cancer patients restores the natural system activity of anti-tumour immunity and promotes the localization of the cancer process.

associated with compromising their anti-tumour immunity. In this regard, early detection and relief of psychoemotional disorders in cancer patients with a psychogenic medical history could prevent the transition of these patients to the category of advanced cancer patients. At the same time, advanced cancer patients with a psychogenic medical history may have a more favourable prognosis after they receive pathogenetically substantiated psychoimmunological treatment.

5. Further research

Clinical practice shows that there are always those with frequent inexplicable recurrences of cancer, resistance to cancer therapy, rapid generalization of the cancer process and common side effects of cancer treatment. Many of these cancer patients are likely to be those with a psychogenic medical history. In order to conduct the successful treatment of such difficult cancer patients, the efficient impact on higher nervous activity of extensive drug and non-drug resources is required. The psychogenic factor is a major pathogenic

factor in cancer patients with a psychogenic medical history (psychogenic carcinogenesis), which operates continuously at all stages of cancer, unlike chemical, physical and biological carcinogenesis. This is particularly important for clinical practice, since it makes it possible to develop a new approach to pathogenesis-based therapeutic-diagnostic and rehabilitation cancer therapies (see Figure 9).

At the diagnostic stage, the group of cancer patients for which the psychogenic factor is pathogenetically significant can be distinguished. For this patient group we earlier proposed the clinical criteria of psychogenic carcinogenesis and developed a diagnostic test for the evaluation of the specific anti-tumour activity of the immune system [25]. At this stage, as in the subsequent stages of cancer, the integrative-oncology approach is required, involving psychiatric or clinical psychological assistance.

At the therapeutic stage, the purposeful detection of mental disorders in cancer patients and their efficient elimination in combination with the standard therapy of cancer is required. It is necessary to develop new drugs in order to conduct standard cancer therapy with a simultaneous impact on higher nervous activity in cancer patients. The development of new drugs and approaches to block the reparative orientation of the immune system in cancer patients is also required. Perhaps this will be the application of low doses of cytotoxic drugs in combination with nonsteroidal anti-inflammatory drugs and other drug combinations.

New approaches to advanced cancer management

Diagnostic stage

Detection of cancer patients group for which the psychogenic factor is pathogenetically significant (criteria of psychogenic carcinogenesis: evaluation of specific anti-tumour activity of the immune system + psychogenic medical history + mental state assessment in cancer patients).

Stage of treatment (classical treatment)

- I. Identification and elimination of mental disorders in cancer patients during the cancer treatment.**
- II. Development and application of new anti-cancer drugs combinations:**
 - 1. Chemotherapy drug + psychotropic drug**
 - 2. Chemotherapy drug + neuroprotective drug**
 - 3. Chemotherapy drug + psychotropic drug + neuroprotective drug**
 - 4. Immunotropic drug + psychotropic drug**

III. Development and application drugs for blocking of «cancer reparative trap» including conditions after surgery, chemo- and radiotherapy:
For example: Cytostatic drug (low doses) + NSAIDs and other combinations.

Additional cancer treatment and stage of cancer rehabilitation

Anti-relapse psycho-immunological treatment for cancer patients with psychogenic medical history (psychogenic carcinogenesis).

Figure 9. Future promising clinical approaches to advanced cancer treatment.

At the additional cancer treatment stage and stage of cancer rehabilitation it is necessary to preserve mental health and the specific anti-tumour activity of the immune system. In this regard, we have developed and tested an anti-relapse psychoimmunological approach to the treatment of advanced cancer patients with a psychogenic medical history using a special method of

hypnotherapy and original techniques of epicutaneous and extracorporeal activation of specific anti-tumour immunity.

Thus, the early diagnosis of cancer patients with psychogenic medical history and the use of pathogenesis-based cancer treatment will allow reducing financial costs and improving the results of cancer treatment.

6. Conclusion

The present study revealed there to be a special group of advanced cancer patients by the presence of their psychogenic medical history, comorbid psychoemotional disorders, and suppressed specific anti-tumour activity of the immune system. The above mentioned characteristics, we believe, are the clinical criteria of psychogenic (stressful) carcinogenesis [25]. Therefore, the comorbid psychoemotional disorders of this group of advanced cancer patients have a major influence on the course and outcome of the cancer disease. These patients need to receive a special psychoimmunological treatment, consisting of two strictly sequential steps: elimination of psychoemotional disorders, and activation of specific anti-tumour immunity. At the same time, the impossibility of the sustained relief of psychoemotional disorders in advanced cancer patients at the first stage of cancer treatment excludes a further transition to the immunoactivation stage, and can be considered to be an adverse prognostic factor with regard to the lives 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 interesting to various professionals involved in treating advanced cancer patients.

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