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Psychogenic activation phenomenon of specific anti-tumor immunity in cancer patients

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The present study aimed to identify the influence of the mind on specific anti-tumor immunity of cancer patients. The study involved 90 cancer patients (78 women and 12 men) with 18 various types of cancer. The presence of psychogenic medical history before diagnosis of cancer was the basic criterion of cancer patients selection for this study. The psychometric parameters, quality of life, delayed-type hypersensitivity skin reaction on the tumor-associated antigens of human melanoma cell line BRO, cytokines (30 Plex) in native plasma and 24 h blood supernatants were investigated before and after psycho-correction. The delayed-type hypersensitivity skin reaction on the tumor-associated antigens in all cancer patients significantly increased ($p= 0.0001$) after elimination of psycho-emotional disorders by psychotropic drugs. In this case, there were no detected reliable changes in the concentrations of cytokines. The described new pathophysiological phenomenon consists in a spontaneous (non-immunogenic) increase of specific anti-tumor activity of the immune system of cancer patients who coped effectively with psycho-emotional disorders.

Key words: Cancer patients, specific anti-tumor immunity, delayed-type hypersensitivity reaction, psychogenic medical history, psycho-emotional disorders.

INTRODUCTION

The cancer process is still uncontrollable (Boyle and Ferlay, 2005; Herbst et al., 2006), despite significant progress in understanding of cancer biology (Coleman and Tsongalis, 2006). Largely, it is caused by unpredictability of the state of anti-tumor immunity of cancer patients at all stages of the cancer disease course and the difficulty of its valid and reliable evaluation (Armstrong and Hawkins, 2001). It is understood that the appearance of cancer and the lack of its recurrence depends on the supervisory functions of the immune system, and its specific anti-tumor activity (Kim et al., 2007). Earlier, attention was drawn to the possibility of forming psychogenic induced immunosuppression in cancer patients (Kiecolt-Glaser et al., 2002). In addition, there were shown relationships between the activity of NK-cells,

psychological factors and the activity of cerebral cortex and the limbic system. In particular, in observing patients with various malignant tumors, a reduction of cerebral metabolism was noted in the limbic brain structures (Tashiro et al., 2001), ensuring the formation of motivations, emotions, and behavioral reactions, appropriate adaptation of the body to the external environment and the preservation of homeostasis.

There is some reason to believe that the huge potential of the brain is capable to supervise and modulate the processes connected with genesis and progression of cancer (Mravec et al., 2008). We have repeatedly observed in our clinical practice that effective treatment of psycho-emotional disorders of cancer patients with psychogenic medical history was followed by disease-free

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survival. This disease-free survival would not be possible without active participation of anti-tumor immunity. It is known that cancer patients with high levels of functional activity of cytotoxic T lymphocytes and natural killer cells exhibit longer terms of survival (Blake-Mortimer et al., 2004). However, the relationship of a specific anti-tumor activity of the immune system and higher nervous activity in cancer patients was not clear yet. The purpose of this study was to investigate the possibility of the mental state influence to a specific anti-tumor activity of the immune system of cancer patients.

METHODOLOGY

Ethical approval for this study was obtained at the Ethical Committee of the Institute of Clinical Immunology, Siberian Branch of the Russian Academy of Medical Sciences (Novosibirsk, Russian Federation), protocol No. 48, April 8, 2010. All patients gave written informed consent.

Characteristics of cancer patients

The presence of psychogenic medical history before diagnosis of cancer was the basic criterion of selection of cancer patients. Psychogenic medical history was studied for each patient in anamnesis morbi (history of present illness) and included the presence of massive traumatic events (death of a close person, divorce, appearance of the disabled person in family, frequent family conflicts, change of residence and work, etc.) with the formation of helplessness, hopelessness, despair. The study involved 90 cancer patients (78 women and 12 men) with 18 cancers: breast cancer [34 (37.8%)], ovarian cancer [10 (11.1%)], melanoma [6 (6.7%)], uterine cancer [6 (6.7%)], kidney cancer [6 (6.7%)], rectal cancer [5 (5.6%)], colon cancer [4 (4.4%)], other sites (cervical, vulva, stomach, lung, bladder, thyroid, laryngis, pleural mesothelioma, lymphoma, lymphosarcoma, acute myeloblastic leukemia) [19 (21%)]. Cancer stage: I [15 (16%)], II [33 (35%)], III [26 (29%)], IV [16 (19%)]. Age characteristics: 30 to 40 years [6 (6.7%)], 41 to 50 years [27 (30%)], 51 to 60 years [41 (45.5%)], over 61 to 70 years [11 (12.2%)], 71 to 80 years [5 (5.6%)] patients. Smokers [17 (18.9%)] and non-smokers [73 (81.1%)]. All patients were administered the standard combined treatment for malignant tumors: only surgery [39 (43.3%)], surgery and chemotherapy [26 (28.9%)], surgery, chemotherapy and radiotherapy [14 (15.7%)], surgery and radiotherapy [4 (4.4%)], only chemotherapy [4 (4.4%)], only chemo- and radiotherapy [1 (1.1%)] patients. No treatment was given to 2 (2.2%) of patients. The time after surgery varied from 1 month to 12 years and among those from 1 month to 1 year [42 (50.6%)], 1 to 3 years [25 (30.1%)], 3 to 5 years [10 (12%)]; and over 5 years [6 (7.3%)].

Forty-five patients of the 90 cancer patients after elimination of psycho-emotional disorders by psychotropic drugs agreed to participate in further studies. This group ($n = 45$) included: 39 women and 6 men with 12 cancer types: breast cancer [17 (37.8%)], ovarian cancer [6 (13.3%)], uterine cancer [5 (11.1%)], melanoma [4 (8.9%)], kidney cancer [4 (8.9%)], colon cancer [3 (6.7%)], and one patient each with rectal cancer, stomach cancer, cervical cancer, bladder cancer, lung cancer and cancer laryngis [6 (13.3%)]. Cancer stage include: I [10 (22.2%)], II [15 (33.4%)], III [14 (31.1%)], and IV [6 (13.3%)]. Age characteristics: 30 to 40 years [4 (8.9%)], 41 to 50 years [18 (40%)], 51 to 60 years [19 (42.2%)], 61 to 70 years [3 (6.7%)], 71 to 80 years [1 (2.2%)] patients. Smokers [9 (18.9%)] and non-smokers [36 (81.1%)]. All patients

were randomly assigned after the completion of the standard combined treatment of malignant tumors: only surgery [21 (46.7%)], surgery and chemotherapy [14 (31.1%)], surgery, chemotherapy and radiotherapy [7 (15.6%)], surgery and radiotherapy [1 (2.2%)], and only chemotherapy [2 (4.4%)] patients. The time after surgery varied from 1 month to 12 years and among them from 1 month to 1 year were [26 (58.1%)], 1 to 3 years [11 (23.3%)], 3 to 5 year [7 (16.3%)]; and over 5 years [1 (2.3%)].

Psychometric testing and quality of life investigation in cancer patients

The diagnosis of psycho-emotional disorders along with evaluation of psycho-correction was carried out by clinical method with additional usage of the following psychometric tests and rates: Hospital anxiety and depression scale (HADS) for anxiety and depression; State-trait anxiety inventory scale (STAI) for stait anxiety and trait anxiety; Symptom Checklist 90 (SCL-90) for somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, and global severity index. The quality of life was measured with the 36-Item short form health survey (SF-36) for physical functioning, role-physical functioning, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.

The psychotropic medicines in psycho-correction of cancer patients

The main purpose of adjustment of psycho-emotional disorders by psychotropic drugs was the complete elimination of psycho-emotional disorders in cancer patients. The following medications were used: coxal (tianeptine), valdoxan (agomelatine), velaxin (venlafaxine), fluoxetine, afobazol, diazepam (microdoses). Mental disorders treatment was carried out strictly individually. In case of the absence of the clinical effect or the occurrence of side effects, the drug and treatment scheme were replaced.

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

Anti-tumor activity of the immune system of cancer patients 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 in the amount of 25 thousand cells in a test. Human melanoma cell line BRO (Lockshin et al., 1985) 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.

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

The human melanoma cell line BRO were maintained in Roswell Park Memorial Institute (RPMI) 1640 supplemented with 10% heat-inactivated fetal calf serum, L-glutamine (2 mmol/ml), 25 mmol hydroxyethyl piperazineethanesulfonic acid (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-Ethylenediaminetetraacetic acid (EDTA) followed by washing three times with Dulbecco's phosphate-buffered saline (DPBS), 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 -20°C until use.

Multiplex cytokine analysis (Human 30-Plex)

Multiplex testing service (Human Cytokine Panel 30-Plex, 96 Assay-Points): IL-1 β , IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p40/p70), IL-13, IL-15, IL-17, TNF- α , IFN- α , IFN- γ , GM-CSF, MIP-1 α , MIP-1 β , IP-10, MIG, Eotaxin, RANTES, MCP-1, VEGF, G-CSF, EGF, FGF-basic, HGF, was carried out in Institute of Medical Microbiology and Hygiene, Regensburg, Germany. The materials for investigation were native plasma and 24 h blood supernatants in cancer patients before and after adjustment of psycho-emotional disorders by psychotropic drugs. In order to obtain this, the blood supernatant was used in RPMI 1640 medium in a 1:4 ratio followed by cultivating at 37°C in atmosphere with 5% CO₂. The native plasma and 24 h blood supernatant samples were stored at -80°C until analysis.

Statistical analysis

The statistical data processing was done using ALGLIB numerical analysis and data processing library which is available to the public. The minimal p-value in this library is 0.0001. The level of statistical significance (so-called alpha level for a p-value) was accepted as 0.05. Because majority (> 50%) of parameters under investigation were not normally distributed (by Kolmogorov-Smirnov test), a non-parametric test procedure was used. For all tests, two-tailed modifications were considered. Wilcoxon signed-rank test was used to find differences in mean values of psychometric and immunologic parameters before and after psycho-correction. To study relationship between psychometric and immunologic parameters, correlation analysis was done by Spearman's rank correlation test.

RESULTS

Psycho-emotional disorders in cancer patients with psychogenic medical history

Clinical and psychometric studies of 90 cancer patients with psychogenic medical history showed that 95.6% of patients have had various psycho-emotional disorders. According to ICD-10, the disorders distribution was as follows: generalized anxiety disorder (F41.1) [31 (36.0%)], mixed anxiety and depressive disorder (F41.2) [10 (11.6%)], prolonged depressive reaction (F43.21) [10 (11.6%)], mixed anxiety and depressive reaction (F43.22) [28 (32.6%)] and organic anxiety disorder (F06.4) [7 (8.2%)] which in our opinion was a complication chemotherapy. It should be noted that 4 out of 90 cancer patients had no psycho-emotional disorders, and simultaneously registered higher indicators of DTH skin reaction (hyperemia diameter 15 to 16 mm). There were three cancer patients with breast cancer and one with colon cancer, in which time after surgery was an average of 4.8 years. There were 100% of mental disorders in the group of 45 cancer patients who agreed to participate in further studies. According to ICD-10, structure of disorders

was as follows: generalized anxiety disorder (F41.1) [17 (37.8%)], mixed anxiety and depressive disorder (F41.2) [2 (4.4%)], prolonged depressive reaction (F43.21) [2 (4.4%)], mixed anxiety and depressive reaction (F43.22) [20 (44.5%)] and organic anxiety disorder (F06.4) [4 (8.9%)], which in our opinion was a complication chemotherapy which is also called 'chemo brain' phenomenon (Staat and Segatore, 2005).

Results of adjustment of psycho-emotional disorders in cancer patients with psychogenic medical history

The main purpose of therapy was the complete elimination of psycho-emotional disorders in cancer patients using the psychotropic drugs. This psycho-correction was followed by achievement of significant clinical effects, which are confirmed by data of psychometric measurement. Results are shown in Table 1. In addition, the improvement of cancer patients' quality of life was achieved on the background of psycho-correction. Results are shown in Table 2. It should be noted that the process of drug correction of psycho-emotional disorders in cancer patients has been fraught with considerable difficulties. It was often necessary to change an antidepressant for several times or to combine it with anxiolytic. The greatest clinical benefit was obtained by the combined administration of the following drugs: coxal (tianeptine), 1 tablet 3 times a day and diazepam, 1/6 tablet (microdoses) 3 times a day. The duration of this treatment regimen is 2 to 3 months. In general, the duration of the treatment course with other drugs to achieve the desired clinical effect varied widely, from 1 through 6 months.

Psychogenic activation phenomenon of specific anti-tumor immunity in cancer patients with psychogenic medical history

It was observed that there was no or minimal (hyperemia diameter before 2 mm) DTH skin reaction to the TAA of human melanoma cell line BRO before the beginning of psycho-correction in almost all cancer patients regardless of the cancer type, cancer stage and time after surgery. The peak response to BRO cell line lysate in most cases (the diameter of redness in mm) was observed after 12 h. Results are shown in Table 3. The DTH skin reaction in all cancer patients significantly increased from 2.62 \pm 0.54 to 7.80 \pm 0.96 mm after effective psycho-correction (Figure 1). The DTH skin reactions to administration of TAA according to the ages of cancer patients are shown in Table 4. The degree of immune responses of 30 to 50 years old and 51 to 60 years old cancer patients were not different. The degree of immune response against TAA

Table 1. Psychometric indicators in cancer patients before and after treatment of psycho-emotional disorders.

Indicator	Before (n=45) Mean±SEM*	After (n=45) Mean±SEM*	P
Symptom checklist 90 (SCL-90)			
Somatization	1.31±0.10	0.90±0.10	0.0001
Obsessive-Compulsive	1.16±0.10	0.74±0.08	0.0001
Interpersonal Sensitivity	0.95±0.16	0.60±0.09	0.0001
Depression	1.36±0.11	0.82±0.08	0.0001
Anxiety	0.91±0.09	0.66±0.13	0.0001
Hostility	0.77±0.09	0.52±0.08	0.0001
Phobic Anxiety	0.47±0.07	0.26±0.07	0.0014
Paranoid Ideation	0.67±0.08	0.56±0.08	0.0002
Psychoticism	0.74±0.09	0.50±0.07	0.0001
Global Severity Index	1.00±0.07	0.60±0.05	0.0001
Hospital anxiety and depression scale (HADS)			
Anxiety	9.37±0.63	4.44±0.46	0.0001
Depression	7.62±0.64	3.28±0.54	0.0001
State-trait anxiety inventory scale (STAI)			
Stait Anxiety	39.16±1.65	28.58±1.95	0.0001
Trait Anxiety	40.82±1.63	29.95±1.87	0.0001

*Means and standard errors means .

Table 2. Quality of life (SF-36) in cancer patients before and after treatment of psycho-emotional disorders.

Indicator	Before (n=45) Mean±SEM*	After (n=45) Mean±SEM*	P	
Physical health	Physical functioning	68.29±3.45	79.29±2.49	0.0006
	Role-physical functioning	29.27±6.47	58.57±5.07	0.0002
	Bodily pain	52.73±3.92	73.74±2.93	0.0003
	General health	41.66±3.42	56.80±2.81	0.0012
Mental health	Vitality	45.98±3.69	67.00±2.31	0.0001
	Social functioning	57.85±4.49	82.06±2.15	0.0001
	Role-emotional	35.78±6.23	64.77±5.11	0.0004
	Mental health	44.59±3.47	69.31±1.78	0.0001

*Means and standard errors means.

Table 3. Dynamics of DTH skin reaction on TAA of human melanoma cell line BRO (hyperemia diameter, mm) before and after treatment of psycho-emotional disorders.

Time after administration (h)	Before (n=45) Mean±SEM*	After (n=45) Mean±SEM*	P
9	3.13±0.74	7.43±0.87	0.0001
12 (peak response)	2.62±0.54	7.80±0.96	0.0001
24	1.67±0.44	5.74±0.72	0.0001

*Means and standard errors means.

of 61 to 80 years old cancer patients is difficult to assess because of the small number of patients (n = 4).

In the correlation analysis were identified inverse connection between psychometric parameters "stait

anxiety" (r = -0.22, p = 0.047), "psychoticism" (r = -0.22, p = 0.041) and indicated the activity of specific anti-tumor immunity of cancer patients (DTH skin reaction on the TAA). At the same time, was found a positive correlation

Table 4. DTH skin reaction on TAA of human melanoma cell line BRO (hyperemia diameter, mm) before and after psycho-correction according to the ages.

Age (years)	Before (Mean±SEM*)	After (Mean±SEM*)	P
30-50 (n=22)	1.73±0.41	7.86±1.07	0.0001
51-60 (n=19)	2.72±0.68	7.11±1.05	0.0001
61-80 (n=4)	5.00±3.79	6.75±1.93	2.7670 ^{NS}

*Means and standard errors means; ^{NS}p>0.05 not significant at 5%.

Table 5. Cytokines in native plasma of cancer patients before and after treatment of psycho-emotional disorders by psychotropic drugs.

Cytokines in native plasma (pg/ml)	Before (n=45) Mean±SEM*	After (n=45) Mean ±SEM*	P
VEGF	8.380±0.94	6.830±0.80	0.679 ^{NS}
EGF	34.99±7.16	28.20±7.81	0.778 ^{NS}
HGF	199.2±41.0	204.1±75.3	1.000 ^{NS}
FGF-basic	17.62±4.01	10.84±1.19	0.383 ^{NS}
IL-2R	232.5±16.3	226.3±30.5	0.552 ^{NS}
IL-6	13.03±2.63	15.44±5.55	0.585 ^{NS}
IL-8	152.1±47.7	128.9±42.3	0.769 ^{NS}
IL-12p40/p70	59.09±3.76	54.78±4.19	0.835 ^{NS}
RANTES	1732.5±133.9	1872.5±190.8	0.766 ^{NS}
Eotaxin	47.98±2.94	48.44±5.95	0.795 ^{NS}
MIP-1alpha	48.21±8.46	46.63±9.75	0.771 ^{NS}
MIP-1beta	70.50±11.7	68.34±14.9	0.989 ^{NS}
MCP-1	635.6±31.5	605.9±36.8	0.742 ^{NS}
TNF-alpha	11.36±4.19	17.86±8.52	0.188 ^{NS}
IP-10	49.90±5.08	38.07±3.94	0.809 ^{NS}
MIG	57.60±7.97	51.15±7.56	0.320 ^{NS}

*Means and standard errors means; ^{NS}p > 0.05 not significant at 5%.

correlation between “mental health” (the SF-36) and the DTH skin reaction ($r = -0.46$, $p = 0.003$). The specific anti-tumor activity of the immune system is associated with mental health as well as anxiety which is an obligate symptom in cancer patients (Miller and Massie, 2006).

The native plasma of cancer patients from 30 examined cytokines were very low, far below the lower limits of detection concentrations following 14 cytokines: IL-1b, IFN α , IL-1RA, IL-2, IL-4, IL-5, IL-7, IL-10, IL-13, IL-15, IL-17, G-CSF, GM-CSF, IFN- γ . A 24 h blood supernatants of 30 cytokines could not determine the concentration of the following 13 cytokines: IFN α , IL-2, IL-4, IL-5, IL-7, IL-10, IL-13, IL-15, IL-17, G -CSF, GM-CSF, IFN- γ , MIG. Comparative analysis showed no significant change in the concentrations of studied native plasma cytokines and 24 h blood supernatants before and after treatment ($P>0.05$). Results are shown in Table 5 and Table 6. In addition, levels of cytokine concentrations did not

correlate with DTH skin reaction before and after psycho-correction of cancer patients.

DISCUSSION

In our opinion, cancer patients with psychogenic medical history are affected by both massive psycho-trauma: stressful life events such as before cancer diagnosis and the fact of a cancer diagnosis itself. These circumstances explain the high level (95.6%) of psychopathology in cancer patients with psychogenic medical history. We assumed that these cancer patients, regardless of the type of cancer, have both psychologically caused psycho-emotional disorders, and psychologically caused depression of anti-tumor immunity. This provision became the basis for psycho-immunological studies of cancer patients in one group, without dividing them into separate

Table 6. Cytokines in 24 h blood supernatants of cancer patients before and after treatment of psycho-emotional disorders by psychotropic drugs.

Cytokines in 24h blood supernatants (pg/ml)	Before (n=45) Mean±SEM*	After (n=45) Mean±SEM*	P
VEGF	10.08 ± 1.18	12.49 ± 2.41	0.483 ^{NS}
EGF	19.71 ± 1.51	23.06 ± 2.22	0.094 ^{NS}
HGF	75.95 ± 4.43	71.88 ± 6.32	0.654 ^{NS}
FGF-basic	15.91 ± 0.56	14.92 ± 0.84	0.234 ^{NS}
IL-2R	84.9 ± 12.3	123.3 ± 29.0	0.154 ^{NS}
IL-6	143.4 ± 63.8	346.2 ± 150.3	0.137 ^{NS}
IL-8	600.1 ± 230.6	2057.4 ± 738.4	0.084 ^{NS}
IL-12p40/p70	84.67 ± 11.7	105.1 ± 18.4	0.194 ^{NS}
RANTES	1143.0 ± 97.3	1571.7 ± 230.2	0.496 ^{NS}
Eotaxin	31.44 ± 1.69	30.29 ± 1.96	0.826 ^{NS}
MIP-1alpha	222.7 ± 97.8	801.2 ± 418.9	0.269 ^{NS}
MIP-1beta	515.7 ± 215.3	1595.1 ± 600.7	0.300 ^{NS}
MCP-1	401.6 ± 118.9	753.3 ± 236.3	0.928 ^{NS}
TNF-alpha	48.24 ± 20.1	73.83 ± 27.3	0.191 ^{NS}
IL-1RA	282.5 ± 67.9	501.8 ± 144.2	0.313 ^{NS}
IP-10	28.11 ± 2.91	20.46 ± 1.98	0.898 ^{NS}
IL-1β	25.76 ± 7.20	61.53 ± 24.8	0.578 ^{NS}

*Means and standard errors means; ^{NS}p > 0.05 not significant at 5%.

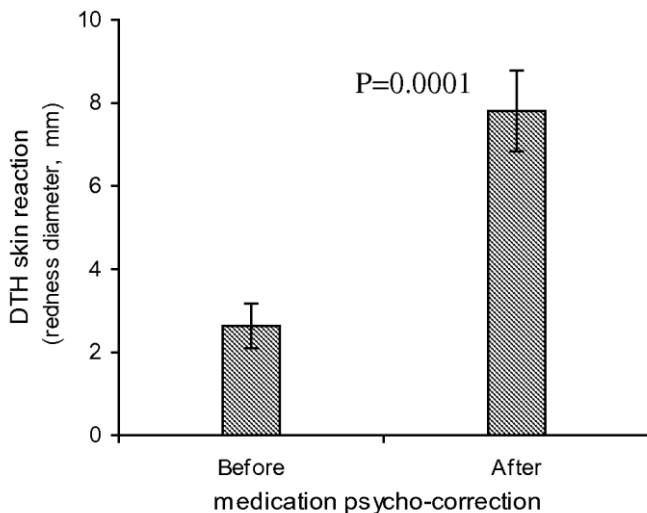


Figure 1. Increase of the delayed type hypersensitivity reaction on tumor-associated antigens in cancer patients background medication psycho-correction. Initially suppressed specific anti-tumor immunity (low DTH skin reaction on tumor-associated antigens) in cancer patients with psychogenic anamnesis was activated (increase in performance DTH skin reaction) as a result of effective medication of the psycho-emotional disorders.

nosologies. The time spent on adjustment of psycho-emotional disorders of cancer patients with psychogenic medical history by psychotropic drugs did not depend on

the form of the cancer stage, time after surgery treatment and kind of psycho-emotional disorders.

Another feature was a bad compliance in some cancer patients after the effective cupping of their psycho-emotional disorders. Patients feeling very good and their continued participation in the rehabilitation program did not consider it necessary (perhaps this behavior of cancer patients is associated with psychological and cultural characteristics of the patients).

It is known that there is maximal spectrum of the tumor-associated antigens typical for different histological types of malignant solid tumors expressed on melanoma cells (Wang, 1997). In our preliminary studies, particularly BRO cell line lysate allowed us to obtain maximum DTH skin reaction with the minimum number of cells (in the amount of 25 thousand cells in a test). Selecting a minimum number of TAA to the skin test DTH (according to our preliminary studies) is due to a desire to obtain specific anti-tumor immunological response in cancer patients without their prior vaccination, and without the possibility of vaccine effect in most of the diagnostic test.

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), a diagnostic dose nearly 100 times smaller (2.5×10^4 cells versus 2.4×10^6 cells) was used. In addition, our patients did not receive any immunotropic therapy during the study. The selected dose does not cause allergic and other pathological

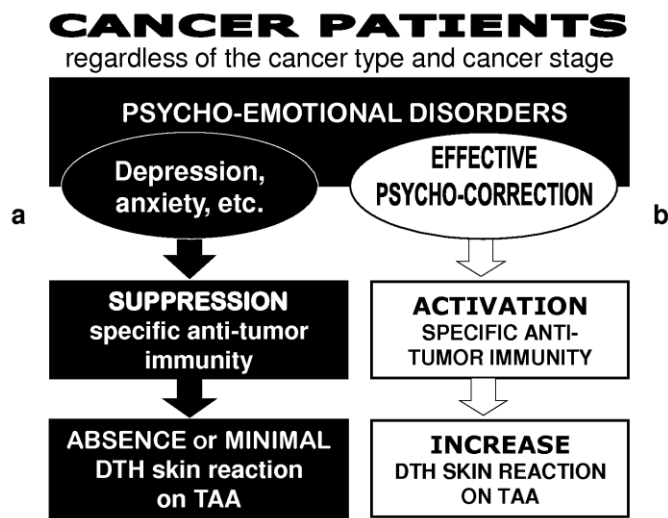


Figure 2. Influence of mind on specific antitumor immunity in cancer patients. (a) Psycho-emotional disorders in cancer patients with psychogenic anamnesis regardless of the cancer type and stage are by suppression of specific anti-tumor activity of the immune system. DTH skin reaction melanoma cell line BRO is the absence or minimal (hyperemia diameter before 2 mm): black part of figure. (b) Effective psycho-correction leads to activation of anti-tumor immunity in cancer patients with a significant increase of DTH skin reaction on TAA of human melanoma cell line BRO: white part of figure.

reactions. It is known that the delayed type hypersensitivity reaction is a specific immune response and begins to manifest later (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, (early 12 h) 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 was achieved (Jacysyn et al., 2001).

It should be emphasized that the increase of specific anti-tumor activity of the immune system in cancer patients with psychogenic medical history as response to elimination of psycho-emotional disorders is the spontaneous reaction of the immune system. So it is not related to preliminary immunostimulation. We believe that such spontaneous reaction of the immune system is the result of elimination of psychogenic immunosuppression. Elimination of psycho-emotional disorders was not accompanied by changes in concentrations of cytokines determined either in native plasma, neither in the 24 h blood supernatants. This is a confirmed data that most cytokines act only over a short distance and their investigation in native plasma and 24 h blood supernatants in cancer patients does not reflect changes in the activity of specific anti-tumor immunity in the presented phenomenon. The present research did not reveal cytokine mechanism of the observed pathophysiological

phenomenon.

In 4 out of 90 cancer patients with psychogenic medical history, we have not found any psychopathology. Anamnestic investigation of these cases showed that in the standard of cancer treatment in these patients, there were spontaneous cupping of psycho-emotional disorders caused by positive changes in their personal life and an active social support. The absence of psychopathology, and high levels of specific anti-tumor activity of the immune system (indicators of DTH skin reaction, 15 to 16 mm) in these cancer patients are likely to have caused favorable course without recurrence of cancer disease in an average of 4.8 years since the surgery. Therefore, the described phenomenon indicated that at cancer patients with psychogenic medical history, the mind plays a key role in suppression of specific anti-tumor immunity (Figure 2). It should be noted that the index of DTH skin reaction used by us as a biological marker is of effectiveness in cupping psycho-emotional disorders in cancer patients.

Conclusion

There are some cancer patients who have psychogenic medical history. Such cancer patients demonstrate extremely high levels of psycho-emotional disorders. However, due to administration of psychotropic drugs, their psycho-emotional disorders disappear and this causes spontaneous (non-immunogenic) increase of specific anti-tumor activity of the immune system determined by specific DTH skin reaction against TAA. These immunological reactions were observed in cancer patients with psychogenic medical history regardless of the cancer type, cancer stage and ages. Discovered new pathophysiological phenomenon requires further, more in-depth study on a larger number of cancer patients including patients without psychogenic medical history. The results of future studies will help to make a certain contribution to the understanding of the hidden mechanisms of cancer disease and cancer management.

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Abbreviations: TAA, Tumor-associated antigens; DTH, delayed type hypersensitivity; IL, interleukin.

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