

Psychoimmunological Analysis of Cancer Patients: Correlation with the Prognosis

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Abstract: Thanks to the discoveries of psychoneuroendocrinology, we now know that every psychological state is mediated by a specific neurochemical condition and every neurochemical change in turn influences psychological status. We can now identify three different levels of neurochemical mediation of the psychological states: neurotransmission, neuromodulation, and the psychoneuromodulation. Neurotransmission is composed of five main neural pathways, noradrenaline, acetylcholine, dopamine, serotonin, and histamine; neuromodulation; and the psychoneuromodulation. We have performed several clinical studies in an attempt to correlate the psychological status of cancer patients with the immune alterations characteristic of the clinical history of neoplastic disease. We have studied the immunologic status by evaluating cytokine blood levels and the lymphocyte subpopulation; the psychological status was assessed by the Rorschach's test; and spiritual status was evaluated by a previously published test to explore spiritual faith. These preliminary psychological studies seem to suggest that a pre-treatment analysis of psychological and spiritual status may predict the efficacy of both chemotherapy and immunotherapy in advanced cancer patients.

Keywords: Psychoneuroimmunology, cancer disease, Rorschach's test.

INTRODUCTION

After a long history of separation between medical and psychological science, thanks to the discoveries of psychoneuroendocrinology (PNEI), we currently know that nothing is either solely chemical or solely psychological, but every psychological state is mediated by a specific neurochemical condition and every neurochemical change in turn influences psychological status [1-5]. As a result, the real importance of PNEI may be to identify through research the neurochemical mediation of emotions and states of consciousness. In theory, this is the promise of PNEI, and to realize that promise of a new means of clinical management of human diseases it is essential to evaluate the same patients from both a neuroimmunobiological and a psychological point of view [6-10]. Formerly, psychosomatic medicine considered the neurovegetative system to be the only mediator between psychological condition and biological function. Instead, recent PNEI discoveries have demonstrated the fundamental role of the immune system in the connection between psychoemotional status and biological function [11, 12]. It has been demonstrated that the immune system is involved not only in the activation of the immune response, but also in the modulation of the principal biological functions, including the cardiovascular system, lipid metabolism, endocrine secretion, and neurological functions [13]. We can now identify three different levels of neurochemical mediation of the psychological states: neurotransmission, neuromodulation,

and the psychoneuromodulation. Neurotransmission is composed of five main neural pathways, noradrenaline, acetylcholine, dopamine, serotonin, and histamine; neuromodulation involves two systems comprising neuroinhibitory and neuroexcitatory activities, mediated by the gaba-A and glutaminergic systems, respectively. Finally, psychoneuromodulation consists of a great number of neural interactions, modulated by three neurochemical systems, the endocannabinoid, opioid, and nitric oxide systems. The interactions among the neurochemical pathways are illustrated in Fig. (1). By transferring this knowledge to the field of medical oncology, we have performed several clinical studies in an attempt to correlate the psychological status of patients with the well-demonstrated immune alterations that characterize the clinical history of neoplastic disease. Obviously, each clinical investigation on humans is based on a previous epistemology of human identity. Our clinical investigation has been performed by considering human identity to be a unification of a trinity constituted from the biological body, the soul, and the spirit [14, 15]. The biological body has been immunologically investigated by evaluating cytokine blood levels and the lymphocyte subpopulation; the psychological status was assessed by the Rorschach's test because of its capacity to investigate the unconscious life of patients [16-21]; finally, the spiritual condition was evaluated by a previously published appropriate test to explore spiritual faith [22].

MATERIALS AND METHODS

We have performed four clinical studies. The first study was planned to investigate the psychological response to the Rorschach test in cancer patients. The study included 138 patients (M/F: 72/66; median age: 60 years, range 26–86),

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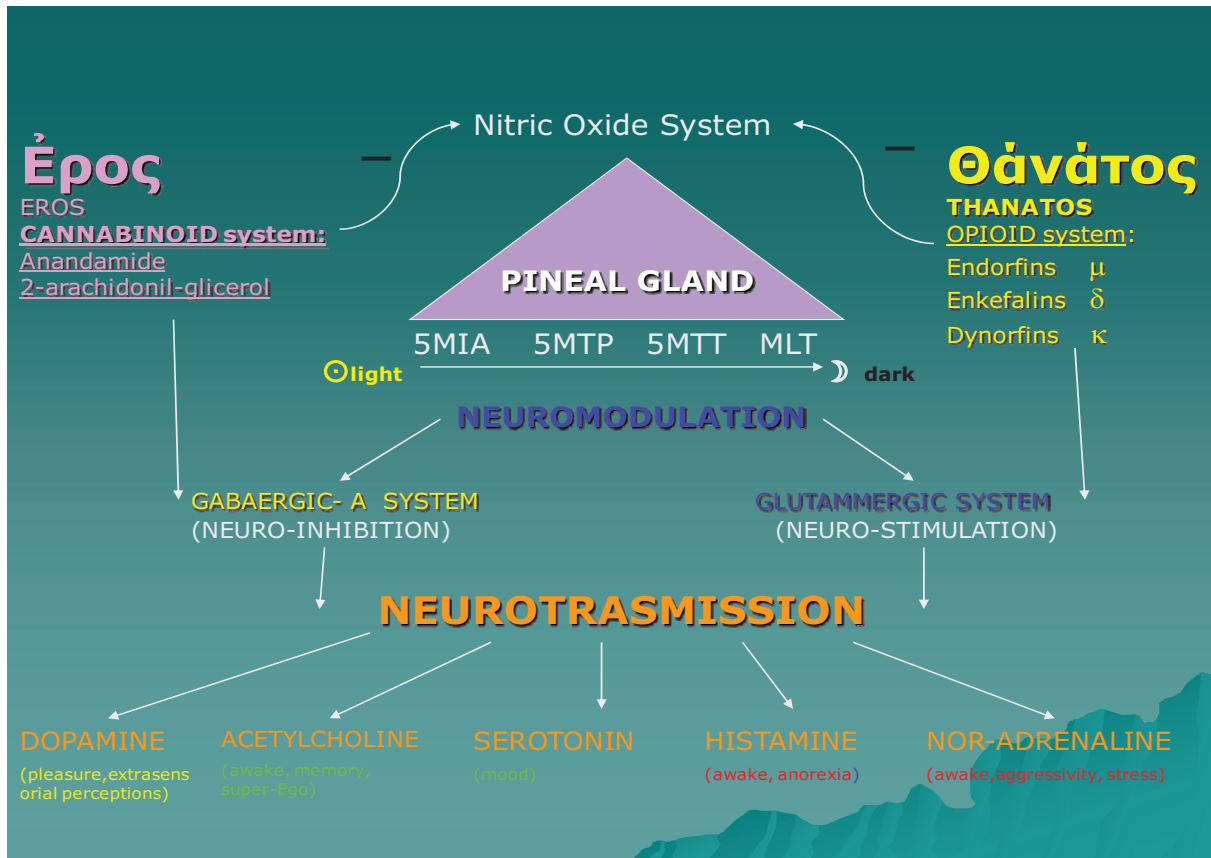


Fig. (1). The psycho-neuro-immunomodulatory network

who were admitted to the Radiation Oncology Division of Monza Hospital from October 2002 to February 2006. Tumor histotypes were as follows: breast cancer, 32; colorectal cancer, 27; non-small-cell lung cancer, 23; renal cancer, 21; endometrial carcinoma, 1; uterine cervical carcinoma, 7; ovarian cancer, 3; prostate cancer, 9; pancreatic cancer, 3; hepatocarcinoma, 2; gastric cancer, 3; biliary tract carcinoma, 1; bladder cancer, 1; testicular cancer, 1; thymic carcinoma, 1; brain glioblastoma, 1; soft tissue sarcoma, 1; melanoma, 1. Distant organ metastases were present in 82 patients (non-small-cell lung cancer, 16; breast cancer, 10; colorectal cancer, 20; renal cancer, 21; prostate cancer, 6; uterine cervical carcinoma, 2; hepatocarcinoma, 2; gastric cancer, 1; melanoma, 1; soft tissue sarcoma, 1; brain glioblastoma, 1; testicular cancer, 1), whereas the other 56 patients presented with disease that was limited to the local area. In a group of 48 cancer patients (breast cancer, 17; colorectal cancer, 17; lung cancer, 15; 24 of whom showed distant organ metastases) the immunological status has been investigated by measuring lymphocyte subsets and serum levels of IL-2 and IL-10. Patients were evaluated before the onset of the various anticancer therapies, including chemotherapy and hormonal therapy.

The second study was planned to evaluate the relationship between psychological status, analyzed using the Rorschach test, and efficacy of IL-2 immunotherapy in the treatment of metastatic renal cell cancer (RCC) patients. The study included 30 metastatic RCC patients. IL-2 was injected

s.c. at a dose of 3 million IU twice/day 5 days/week for 4 consecutive weeks, corresponding to one complete immunotherapeutic cycle, followed by a second cycle after a 21-day rest period. Eligibility criteria were as follows: histologically proven RCC, measurable lesions, no previous therapy for the metastatic disease, no brain metastasis, and no concomitant chronic treatment with drugs influencing the immune system, such as corticosteroids and opioids. In nonprogressing patients, a second cycle was planned after a 21-day rest period. The patients then underwent a maintenance treatment consisting of 5 days of therapy every month, until disease progression or toxicity. Patients were considered evaluable when they received at least one complete immunotherapeutic cycle. The clinical response was assessed according to WHO criteria, undertaking radiological examination before the onset of immunotherapy, after each cycle of immunotherapy, and then at 3-months interval. Visceral metastases were evaluated using CT scan. For hematological analysis, venous blood samples were collected before therapy, at weekly intervals during the immunotherapeutic cycles, and every 3 weeks during the rest period. The third study was conducted in an attempt to correlate the degree of faith obtained to an appropriate spiritual test with the clinical response to chemotherapy, consisting of cisplatin plus gemcitabine and the overall survival time in a group of 50 metastatic non-small-cell lung cancer patients. The eligibility criteria were histologically proven NSCLC; metastatic disease; measurable lesions; no brain metastases; no second tumor; no concomitant important medical illnesses other than cancer; no con-

comitant important psychiatric or psychological disorder or concomitant chronic therapy with psychoactive drugs or agents influencing the immune system, namely opioids and corticosteroids; and no previous chemotherapy or radiotherapy for the metastatic disease. The chemotherapeutic treatment consisted of cisplatin at 100 mg/m² at day 1 plus gemcitabine at 1000 mg/m², at days 1 and 8, every 21 days for at least 3 cycles before repeating the same radiological examinations performed before the onset of chemotherapy, including CT scan, nuclear magnetic resonance (NMR), and/or positron emission tomography (PET). In the patients who did not respond to the first-line chemotherapy, a second line of chemotherapy was planned, consisting of a weekly low-dose of taxotere, followed by only supportive care. Finally, the last study was performed to evaluate regulatory T lymphocyte (CD4⁺CD25⁺) (T reg) number in relation to the response to the Rorschach test in a group of 30 cancer patients suffering from the most frequent tumor histotypes, 21 of whom showed metastatic disease. As far as the immunological evaluation is concerned, venous blood samples were collected in the morning before the onset of the different oncologic treatments. For each blood sample, the absolute number of total lymphocytes, T-helper (CD4⁺), T-cytotoxic (CD8⁺) cells, natural killer (NK) cells (CD16⁺CD56⁺), T lymphocytes (CD3⁺), and T-reg cells (CD4⁺CD25⁺) were assessed. Lymphocyte subsets were measured by a flow cytometry assay, and monoclonal antibodies supplied by Becton-Dickinson (Milan, Italy). The 14 normal values obtained in our laboratory (95% confidence limits) of T-reg lymphocytes and CD4⁺/CD4⁺CD25⁺ were < 240/mm³ and >4, respectively.

The cancer patients were first interviewed of presentation and of anamnesis for about one hour's duration to obtain information concerning social relations, work, previous organic diseases, family, sexuality, spiritual beliefs, childhood experiences, and significant events such as traumas, loss, and affective separations. A second interview was planned to administer the Rorschach test to the cancer patients in order to investigate their psychological profile and to administer the spiritual test in order to investigate their faith. Moreover, a final interview was planned for the restitution of the results obtained from the test, with the possibility of offering those patients with evident psychopathologic disorders follow-up psychotherapy.

The Rorschach test is a projective personality assessment based on the test taker's reactions to a series of 10 inkblot pictures. It is the most widely used projective psychological test. The Rorschach test is used to help assess personality structure and identify emotional problems and mental disorders. It is based on the principle that subjects viewing neutral, ambiguous stimuli will project their own personalities onto them, thereby revealing a variety of unconscious conflicts and motivations. The Rorschach test is used to elicit information about the structure and dynamics of an individual functioning personality. The test provides information about a person's thought processes, perceptions, motivations, and attitudes toward his or her environment, and it can detect internal and external pressures and conflicts as well as illogical or psychotic thought patterns. The Rorschach test is administered using 10 cards, each containing a complicated inkblot pattern, five in black and grey, two in black and red,

and three in various pastel colors. Subjects look at the cards one at a time and describe what each inkblot resembles. They are instructed to look at the shape, shading, and color of the inkblots. After the subject has viewed all 10 cards, the examiner usually goes back over the responses for additional information. The subject may be asked to clarify some responses or to describe which features of each inkblot prompted the responses. There is no one correct response to any inkblot card, although there are certain common responses to some cards. Despite much criticism, the Rorschach test is considered an adequate contribution to psychological diagnosis and study of the profile of the unconscious personality [23].

The clinical approach to investigating spiritual faith consisted of the evaluation of five major criteria. In order to establish a high faith score, obviously, the first criterion is the patient's complete consciousness of the diagnosis of metastatic cancer and of the severity of its prognosis, because if the patient is not aware of a poor prognosis, a designation of high faith status would simply be an emotional illusion. High faith status is the opposite of anxiety, so clinical evidence of exaggerated anxiety would exclude a genuine status of faith. The intellectual knowledge of the mechanisms of action of cancer chemotherapy and those mechanisms responsible for cancer progression does not necessarily enhance the efficacy of the chemotherapy itself, so a tendency toward excessive analytical thinking would also exclude a high status of faith, as it would simply represent a psychological defensive reaction. In the same way, exaggerated faith in the professional capacity of the physician in the case of an incurable metastatic disease is another type of illusion, rather than a genuine status of faith. Finally, since the most evident effect of genuine spiritual faith is the perception of the unity of life, with an amplification of spiritual sensitivity, the perception of the patient's own disease as being the only problem, rather than being a personal experience of general human suffering, also excludes the existence of a real status of faith. A value of 20 points was assigned for each positive response to the five criteria, with a total maximum faith score of 100 points. A real (high) status of faith was defined as a score of not less than the 60 (60%).

The results were statistically evaluated using the Chi-square test, Student's *t*-test, and analysis of variance, as appropriate.

RESULTS

As far as the first study is concerned, the responses to the Rorschach test in relation to the histotype of tumor are reported in Table 1. The anxiety was very high in all cancer patients without significant differences with respect to the histotype of tumor (breast cancer: 21/29 (72%); non-small cell lung cancer: 16/20 (80%); colorectal cancer: 21/25 (84%); renal cancer 13/16 (81%); gynaecologic tumors: 10/12 (83%); prostate cancer: 6/9 (67%)), even though it was higher in colorectal cancer patients and gynaecologic cancer patients. As far as the psychological and somatic identity integrity is concerned, no significant difference was observed among the histotypes of tumor, but the percent of lack of identity integrity was greater than 88% in all cancer patients (breast cancer: 28/29 (96%); non-small cell lung can-

cer: 20/20 (100%); colorectal cancer: 23/25 (92%); renal cancer 15/16 (94%); gynaecologic tumors: 12/12 (100%); prostate cancer: 8/9 (89%). In the group of non-small cell lung cancer and gynecologic cancers, no patient showed an identity integrity. The percent of depression observed in non-small cell lung and renal cancer patients was significantly higher than in those affected by breast cancer ($p < 0.05$) and prostate cancer ($p < 0.05$). The percent of suppression of sexuality observed in breast and colorectal cancer patients was significantly higher than in those affected by renal cancer ($p < 0.05$). As far as the spiritual profile is concerned, no statistically significant difference was observed in relation to tumor histotype (breast cancer: 24/29 (83%); non-small cell lung cancer: 18/20 (90%); colorectal cancer: 22/25 (88%); renal cancer 13/16 (81%); gynecologic tumors: 10/12 (83%); prostate cancer: 8/9 (89%). The responses to the Rorschach's test in relation to the extension of disease are reported in Table 2. Statistically significant differences occurred between the groups of patients with locally limited

disease or with metastatic disease in none of the evaluated psychological parameters. Patients with normal performance in the Rorschach test showed a significantly higher number of total lymphocytes, T lymphocytes, T helper lymphocytes, and NK cells compared with patients with an altered psychological response ($p < 0.05$), whereas no difference was found in T cytotoxic lymphocyte mean number. IL-2 and IL-10 mean serum concentrations were lower and higher, respectively, in patients with altered compared with those with normal response to the Rorschach test, even though only the difference in IL-10 values was statistically significant ($p < 0.05$).

As far as the second study is concerned, a complete response (CR) was achieved only in 1/30 (3%) patients. A partial response (PR) was obtained in other 6/30 (20%) patients. Then tumor response rate (CR+PR) was 7/30 (23%) patients. Stable disease (SD) occurred in 14/30 (47%) patients, whereas the other 9/30 (30%) patients had progressive disease (PD).

Table I. Response to the Rorschach test in relation to the histotype of tumors

Histotype	N	Psychological Parameters (%)				
		Anxiety	No Identity Integrity	Depression	Repression of Sexuality	No Spirituality
OVERALL PATIENTS	126					
- BREAST CANCER	29	21 (72%)	28 (96%)	23 (79%)	29 (100%)**	24 (83%)
- NON-SMALL CELL LUNG CANCER	20	16 (80%)	20 (100%)	20 (100%)*	17 (85%)	18 (90%)
- COLORECTAL CANCER	25	21 (84%)	23 (92%)	22 (88%)	23 (92%)**	22 (88%)
- RENAL CANCER	16	13 (81%)	15 (94%)	16 (100%)*	12 (75%)	13 (81%)
- GYNECOLOGIC TUMORS (uterine cervix carcinoma, ovarian cancer, endometrial carcinoma)	12	10 (83%)	12 (100%)	10 (83%)	11 (92%)	10 (83%)
- PROSTATE CANCER	9	6 (67%)	8 (89%)	6 (67%)	8 (89%)	8 (89%)
MISCELLANEOUS	15					
- HEPATOCARCINOMA	2	0	2	2	2	1
- PANCREATIC ADENOCARCINOMA	3	0	3	2	3	3
- GASTRIC CANCER	3	3	3	3	3	3
- BILIARY TRACT CARCINOMA	1	0	1	1	1	1
- BLADDER CANCER	1	0	1	1	0	1
- MELANOMA	1	0	1	1	1	1
- SOFT TISSUE SARCOMA	1	0	1	1	1	1
- BRAIN GLIOBLASTOMA	1	1	1	0	1	1
- THYMIC CARCINOMA	1	1	1	0	1	1
- TESTIS CANCER	1	0	1	0	1	0

* $p < 0.05$ VS PROSTATE CANCER
VS BREAST CANCER

** $p < 0.05$ VS RENAL CANCER

Table 2. Response to the Rorschach test in relation to the extension of disease

Psychological Parameters (%)						
Extension of Disease	N	Anxiety	No Identity Integrity	Depression	Repression of Sexuality	No Spirituality
Overall Patients	126					
- Locally Limited Disease	53 (42%)	39 (73%)	51 (96%)	43 (81%)	50 (94%)	48 (91%)
- Metastatic Disease	73 (58%)	52 (71%)	70 (96%)	64 (88%)	69 (95%)	59 (81%)

Rorschach’s test was accepted by 24/30 (80%) patients, whereas the remaining 6/30 (20%) patients refused the psychological investigation. The presence of a normal integrity identity was observed in only 7/24 (29%) patients who accepted the psychological analysis. As shown, the three groups of patients with a maintenance of integrity identity, with a lack of integrity identity, or who refused the psychological investigation were well balanced for the overall main prognostic variables, including age, (PS) and dominant metastasis sites. Table 3 shows the clinical response to IL-2 immunotherapy in relation to the psychological profile. The tumor response rate obtained in patients with integrity identity was significantly higher with respect to these patients who had no integrity identity or who refused the psychological investigation ($P < 0.05$ and $P < 0.01$, respectively).

As far as the immunobiological response is concerned, as illustrated in Fig. (2), the mean number of lymphocytes observed before the onset of treatment was higher in patients with an integrity identity than in those without identity or in those who refused the Rorschach test, but without statistically significant differences. On the contrary, the mean maximal lymphocyte count achieved in IL-2 immunotherapy in patients with integrity identity was significantly higher with respect to that observed in patient who had no integrity identity or who refused the psychological analysis ($P < 0.01$ and $P < 0.001$, respectively). The mean increase in lymphocyte number observed during IL-2 immunotherapy is illustrated in Fig. (3). The value observed in patients with a maintenance of integrity identity was significantly higher with respect to that observed in patients who had no integrity identity or

who refused the psychological test ($P < 0.05$ and $P < 0.005$, respectively).

As far as the third study is concerned, the evidence of a real status of faith, with values of at least 60%, occurred in 24/50 (48%) of the patients, whereas the remaining 26 patients had values less than 60%. The two groups of patients were balanced for the overall main clinical and prognostic characteristics, including tumor histotype and dominant metastasis sites. In particular, no statistically significant difference was seen between males and females in the percentage of faith scores greater than 60% (18/35(51%) patients with a faith score less than 60% (11/24 (46%) vs. 4/26(16%), $p < 0.01$). Table 4 shows the mean values of the faith score observed. The patients who achieved tumor regression (CR+PR) showed significantly higher mean values of faith score than those of the non-responder patients (SD+PD) (SD: $p < 0.05$; PD: $p < 0.001$). The values of faith score were also higher in the patients with CR than in those who achieved only a PR, but this difference was not statistically significant. Fig. (4) illustrates the lymphocyte mean number observed before and after chemotherapy in relation to the faith score of patients. No significant difference was seen in lymphocyte mean number prior to chemotherapy between patients with or without a faith score higher than 60%. In contrast, the post-chemotherapeutic mean values of total lymphocytes observed in the patients with high faith score were significantly higher with respect to those found in patients with a low degree of faith ($p < 0.01$). Finally, Fig. (5) illustrates the 3-year survival curves of the two groups of patients. The overall survival was significantly longer in the patients with a faith score of at least 60% than in those with values less than 60% ($p < 0.005$).

Table 3. Clinical response (WHO criteria) to IL-2 immunotherapy in relation to the Rorschach test in metastatic renal cell cancer patients

Patients Rorschach test result	n	Clinical response [†]				SD	DC (CR+PR+SD) (%)	PD (%)
		CR	PR	CR + PR (%)				
No integrity identity	17	0	3	3 (18%)	10	13 (76%)	4 (24%)	
Integrity identity	7	1	3	4 (57%)*	3	7 (100%)	0	
Refusal	6	0	0	0	1	1 (17%)	5 (83%)	

[†] CR:complete response; PR:partial response; SD:stable disease; DC:disease control; PD: progressive disease
* $P < 0.05$ sexual vs. no sexual identity, $P < 0.01$ sexual identity vs. Refusal

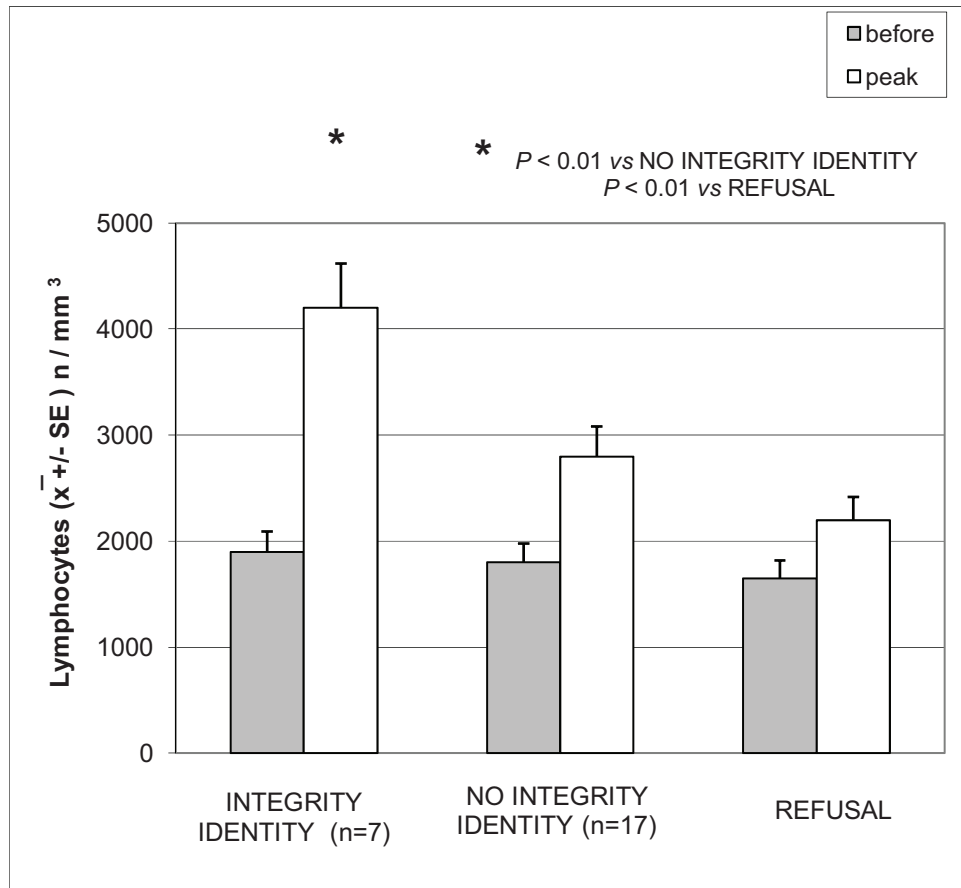


Fig. (2). Mean lymphocyte number before the onset of treatment and mean maximum values during IL-2 immunotherapy in metastatic renal cell cancer in relation to the response to the Rorschach test

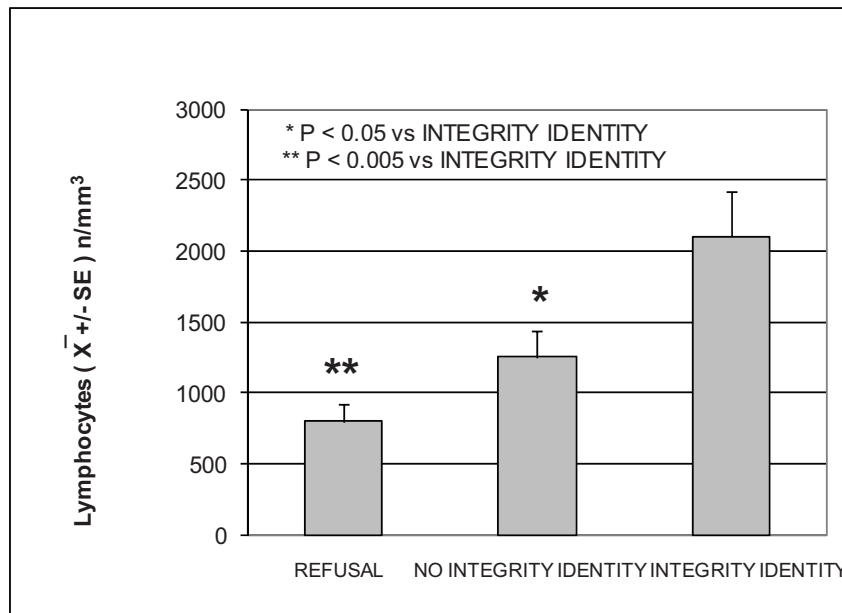


Fig. (3). Mean maximum increase in lymphocyte number observed during IL-2 immunotherapy in metastatic renal cell cancer in relation to the response to the Rorschach test.

Table 4. Faith score (mean±SE) in relation to the clinical response to cancer chemotherapy

Faith Score % (X ± SE)	Clinical response				
	CR	PR	CR+PR	SD	PD
	83±5	71±4	76±4 *	52±5	31±3

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease;
 * $p < 0.05$ vs. SD; $p < 0.001$ vs. PD.

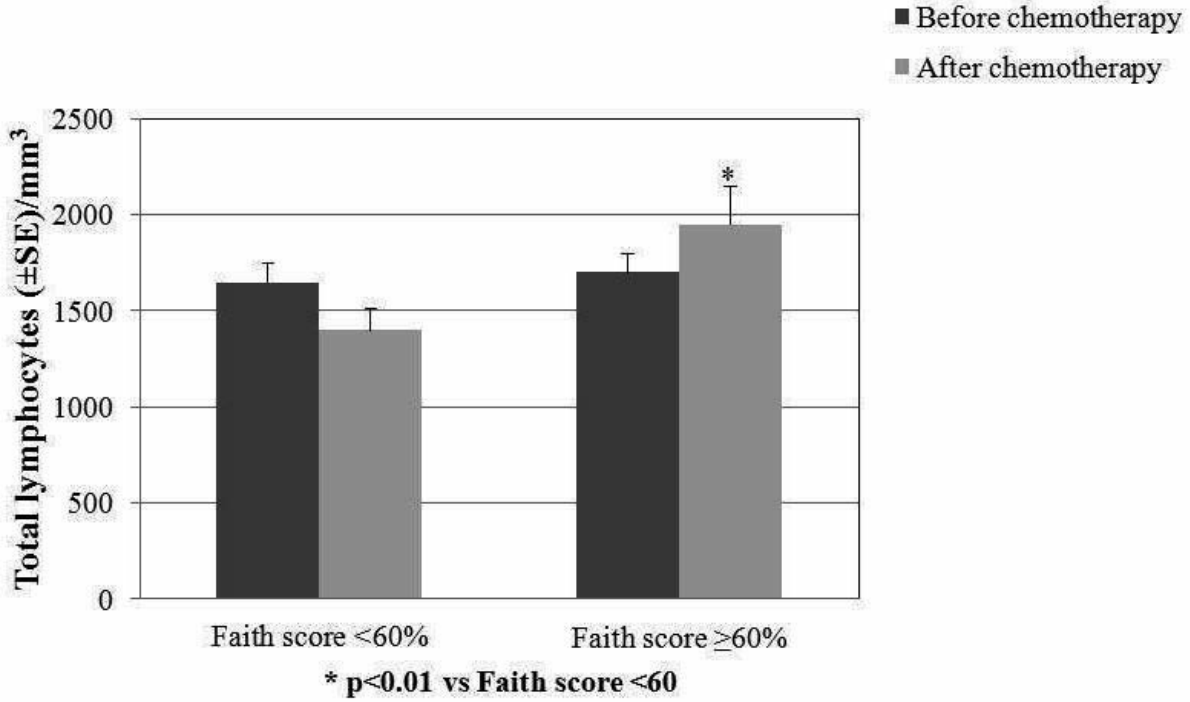


Fig. (4). Lymphocyte mean number observed before and after chemotherapy (cisplatin + gemcitabine) in 50 metastatic non-small cell lung cancer patients with faith score above or below 60%.

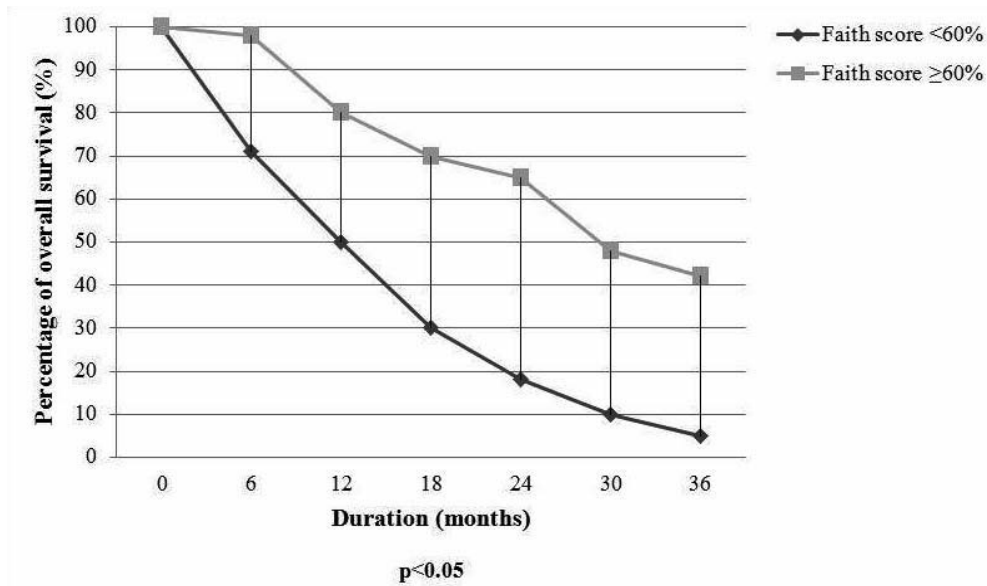
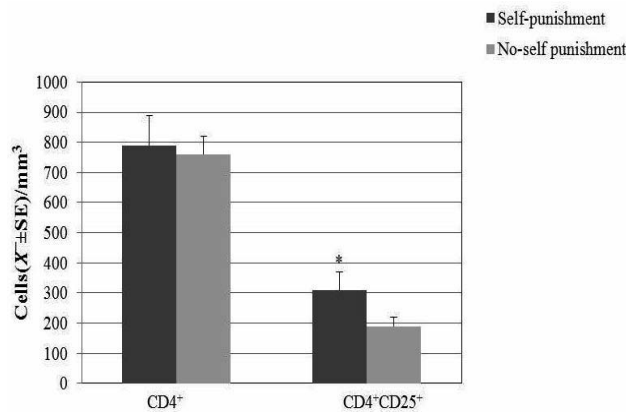


Fig. (5). 3-years survival curves achieved in metastatic non-small cell lung cancer patients in relation to their faith score.

In the last study a psychological profile of self punishment occurred in 18/30 patients (60%). The percentage of patients with abnormally high CD4⁺CD25⁺ values observed in the group with self-punishment was significantly higher than that found in patients without self-punishment (11/18 vs. 3/12, *p*<0.05). Similarly, the percentage of patients with abnormally low values of CD4⁺/CD4⁺CD25⁺ was significantly higher in the group with self-punishment (16/18 vs. 4/12, *p*<0.01). Moreover, as illustrated in Fig. (6), the mean numbers of T-reg lymphocytes observed in the group with self-punishment was significantly higher than that found in patients who had no self-punishment (314±39/mm³ vs. 173±27/mm³, *p*<0.05), whereas no significant difference was seen in the mean number of CD4⁺ cells. In addition, as shown in Fig. (7), the mean CD4⁺/CD4⁺CD25⁺ ratio was significantly lower in patients with self-punishment than in the other group (2.6±0.2 vs. 5.2±0.8, *p*<0.025). Finally, as reported in Table 5, no significant difference in the mean number of total lymphocytes, CD3⁺, CD8⁺ and NK cells was seen between patients with or without self-punishment.

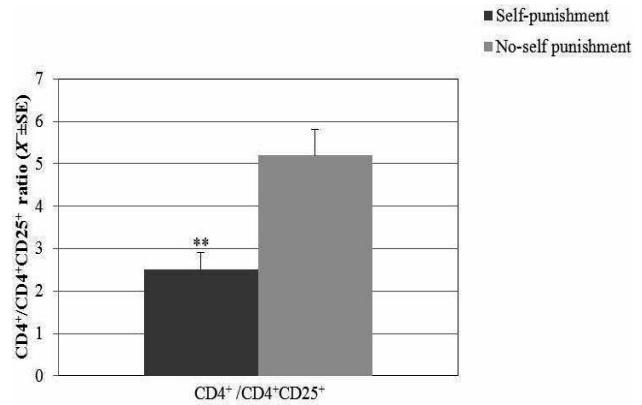
Table 5. Mean numbers of total lymphocytes, T-cytotoxic lymphocytes, NK cells and CD3⁺ cells in cancer patients with or without self-punishment

Lymphocytes (n/mm ³) X ± SE	No self-punishment	Self-punishment
Total lymphocytes	1678 ± 161	1693 ± 91
NK	253 ± 50	269 ± 39
CD3	1230 ± 124	1302 ± 115
CD8	414 ± 49	449 ± 43



p<0.05 vs. No self-punishment

Fig. (6). Mean numbers of T-regulatory lymphocytes (CD4⁺CD25⁺) and T-helper lymphocytes (CD4⁺) in 30 patients with non-metastatic and metastatic solid tumors, with or without presence of self-punishment.



** *p*<0.025 vs. No self-punishment

Fig. (7). Mean CD4⁺/CD4⁺CD25⁺ ratio in 30 patients with non-metastatic and metastatic solid tumor, with or without the presence of self punishment.

DISCUSSION

According to the theoretical basis of PNEI, the results of these studies demonstrate that the so-called psychological problems of cancer patients and their immune and neuroendocrine alterations are not two different entities, but the psychological and the neurochemical condition of the same event, which we now may identify as a consequence of the destruction of the psychobiological life [24-26]. According to the results of these studies, the origin of the destruction is related to the progressive loss of both sensory pleasure and spiritual perception. Obviously, constantly in agreement with the theoretical basis of PNEI, the mediator of the psychobiological destruction is the immune system. In fact, the results of these studies in humans confirm that the response to IL-2 immunotherapy, which historically has been the most effective immunotherapy for cancer, may be predicted by a psychological analysis before the onset of the immunotherapy [27, 28]. In particular, these studies showed the lack of identity and the presence of anxiety negatively influence the response to IL-2 injection in terms of both lymphocyte increase and control of neoplastic growth. The results of these studies also suggest that the psychospiritual status of cancer patients may influence the response to chemotherapy itself, at least in non-small cell lung cancer. This finding is not surprising since it has been demonstrated, according to the PNEI understanding, that the cancer chemotherapy may act not only through a cytotoxic mechanism, but also by modulating the endogenous secretion of cytokines, whose activity determine the efficacy of the anticancer immunity [29-31]. Finally, these results, in contrast to the conventional wisdom which affirms the existence of a lack of an effective anticancer immune response in patients who died from cancer, suggest that cancer patients react immunologically against their cancer, but unfortunately this happens in the form of activation of an immunosuppressive response, mediated by T-reg lymphocytes. Moreover, this result seems to suggest that the

enhanced generation of T-reg lymphocytes is associated or would reflect a particular psychological status, consisting of the evidence of a self-punishment condition. Therefore the psychological approach to cancer patients would not be limited only to a supportive function but also it would have to have a therapeutic impact. In this case, the evaluation of T-reg cell numbers during a psychological therapy could constitute a useful parameter to measure the efficacy of the psychological treatment itself [32].

In conclusion, from the point of view of a preliminary psychological investigation of cancer patients, after several years during which psycho-oncology has been considered a merely supplemental support in the clinical management of cancer patients, the results of these studies would demonstrate the primary importance of the psychoimmunological analysis in the treatment of cancer disease, since it is impossible to effect a real modification of the prognosis of a metastatic cancer patient without a profound change in his psychospiritual life, consisting of a concomitant rediscovery of sensory pleasure and spiritual perception.

SUMMARY

According to the recent discoveries of the psychoneuroendocrinology (PNEI), it has been shown that the prognosis of the neoplastic disease depends not only on tumor histology and disease extension, but also on host anti-tumor immunity. Moreover, since the immune status is under physiological regulatory control by the psychoneuroendocrine system, the antitumor immune response depends on its psychoneuroendocrine regulation. Then, the prognosis of the cancer is influenced by the psychoneuroendocrine conditions of patients. However, as shown by PNEI, the psychoneuroendocrine status simply represents the chemical mediation of the psychological and spiritual status. Therefore, if it is true that the psychoneuroimmune status influences the prognosis of the tumor, it is probable that the psychospiritual condition may affect the prognosis of cancer and the efficacy of the different conventional antitumor treatments. On this basis, we have performed several psycho-oncological studies to analyze the relationship between the psychoimmunological profile and the response to chemotherapy and immunotherapy in cancer patients. The psychological profile was investigated by the Rorschach test. The spiritual status was analyzed in terms of spiritual faith by a specific score evaluating five criteria and giving a value of 20 points for the single parameters. In the first study we evaluated the response to the psychological profile in 138 patients, 48 of whom were immunologically analyzed. The second study included 30 metastatic renal cancer patients in order to evaluate the relationship between the psychological profile and the efficacy of immunotherapy with IL-2. The third study was carried out in 50 advanced non-small cell lung cancer patients in an attempt to correlate the efficacy of chemotherapy to the psychospiritual condition. Finally, we performed a psychoneuroendocrine study to evaluate regulatory T lymphocyte ($CD4^+CD25^+$) number in relation to the Rorschach test response in a group of 30 cancer patients suffering from the most frequent tumor histotypes. As far as the psychological status of cancer patients, we found that anxiety was very high in all cancer patients, as well a lack of psychological and somatic identity integrity. The percentage of pa-

tients in whom depression was observed in non-small cell lung and renal cancer patients was significantly higher than in those affected by breast and prostate cancer. The percentage of breast and colorectal cancer patients who experienced suppression of sexuality was significantly higher than in those affected by renal cancer. A spiritual life was absent in most patients. Patients who showed identity integrity through the Rorschach test showed a significantly higher number of total lymphocytes, T lymphocytes, T helper lymphocytes and NK cells compared to the patients with an altered psychological response. IL-2 and IL-10 mean serum concentrations were lower and higher, respectively, in patients with altered than in those with a normal response to the Rorschach test, even though only the difference in IL-10 values was statistically significant. Moreover, in the third study, the tumor response rate achieved in patients with a high degree of faith was significantly higher than in the other group of patients. The post-chemotherapeutic lymphocyte mean number was significantly higher in patients with evident spiritual faith than in the other patients. Moreover, the percentage of patients achieving a 3-year survival observed in the patients was significantly higher in the patients with a high degree of faith than in patients with a low faith score. In the last study the psychological profile of self-punishment was found in 18/30 patients (60%). The percentage of patients with abnormally high $CD4^+CD25^+$ values observed in the group with self-punishment was significantly higher than that found in patients without self punishment. Similarly, the percentage of patients with abnormally low $CD4^+/CD4^+CD25^+$ values was significantly higher in the group with self-punishment. The mean numbers of T-reg lymphocytes observed in the group with self-punishment was significantly higher than that found in patients who had no self-punishment. In addition, the mean $CD4^+/CD4^+CD25^+$ ratio was significantly lower in patients with self-punishment than in the other group. As expected, these preliminary psychological studies seem to suggest that a pre-treatment analysis of psychological and spiritual status may predict the efficacy of both chemotherapy and immunotherapy in advanced cancer patients. Therefore, if subsequent studies confirm these results, psychological and spiritual evaluations before the onset of conventional anticancer treatments should be included within the usual clinical examination by medical oncologists.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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