

Efficacy of Cancer Chemotherapy in Relation to Synchronization of Cortisol Rhythm, Immune Status and Psychospiritual Profile in Metastatic Non-small Cell Lung Cancer

P. LISSONI¹, G. MESSINA¹, A. BALESTRA¹, M. COLCIAGO²,
F. BRIVIO³, L. FUMAGALLI³, G. FUMAGALLI⁴ and D. PAROLINI¹

*Divisions of ¹Radiation Oncology and ³Surgery, and
⁴Laboratory of Analyses, San Gerardo Hospital, Monza, Milan;
²Laboratory of Analysis, Carate Hospital, Carate, Milan, Italy*

Abstract. *Background: The prognosis of cancer and the efficacy of the various anticancer therapies depend not only on tumor characteristics, but also on the endocrine and immune status of patients. Moreover, studies have shown that the clinical course of the neoplastic disease is also influenced by the psychospiritual status of patients. It is thus probable that the influence of psychospirituality on tumor growth may be mediated by the immunoneuroendocrine system, as demonstrated by the recent advances in psychoneuroendocrinological research. However, at present there are only few data on the possible link between the psychospiritual status and immunoendocrine functions of cancer patients. This study was carried out to investigate the relationships existing among the psychospiritual profile, cortisol rhythm and lymphocyte number before and after chemotherapy, and the efficacy of chemotherapy itself in advanced cancer patients. Patients and Methods: The study included 30 consecutive metastatic non-small cell lung cancer patients under chemotherapeutic treatment with cisplatin plus gemcitabine. The psychobiological investigations consisted of lymphocyte count, cortisol circadian rhythm, psychological profile using Rorschach test, and spiritual score, as assessed by a specific clinical test for spirituality. The control group consisted of 100 healthy volunteers. The patients who achieved a tumor regression, showed a significantly higher pre-treatment lymphocyte count and significantly lower alteration of the cortisol*

rhythm with respect to those who had no benefit from chemotherapy. Moreover, the lymphocyte mean number increased during chemotherapy in responder patients, whereas it progressively diminished in those who had disease progression. Lymphocytopenia and alterations of the cortisol rhythm prior to chemotherapy were associated with a loss of the psychosexual identity according the Rorschach test. Moreover, the mean spiritual score was lower in patients than in controls, although the difference was not significant. Finally, a low spiritual score prior to therapy was associated with a higher frequency of lymphocytopenia and cortisol rhythm alteration, as well as with a lower efficacy of chemotherapy itself. Conclusion: This preliminary study would suggest that the psychospiritual status of cancer patients may influence the efficacy of chemotherapy through the immunoneuroendocrine system.

According to the clinical data available to date, the therapeutic efficacy of cancer chemotherapy may be predicted only on the basis of the characteristics of the neoplastic disease, namely tumor histotype, disease extension and dominant metastasis sites. The prognosis of tumors has also appeared to depend on biological endocrine and immune variables of the patients, mainly on lymphocyte number and function (1-3) and cortisol secretion (4, 5). In fact, lymphocytopenia has been proven to be associated with a poor prognosis in most solid tumor histotypes (6, 7), by representing an index of the immunosuppressive status (8). Moreover, the evidence of an altered cortisol circadian rhythm, which is the expression of a biological desynchronization with respect to environmental conditions, appeared to play an unfavourable prognostic significance (9). In addition, previous studies suggested a physiopathological link between cancer-related lymphocytopenia and an anomalous cortisol rhythm with abnormally high blood

Correspondence to: Dr. Paolo Lissoni, Divisione di Radioterapia Oncologica, Ospedale San Gerardo, 20052 Monza, Milan, Italy. Fax: +39 039 2332284, e-mail: p.lissoni@hsgerardo.org

Key Words: Chemotherapy, cortisol rhythm, lymphocytopenia, psychoncology.

concentrations, because of the inhibitory effect of cortisol on lymphocyte proliferation and functions (10). Finally, very preliminary data seem to show that lymphocyte proliferation and activation may be influenced by the psychological status of the patients (11). Nevertheless, despite the great variety of data showing that the prognosis of the neoplastic disease is also influenced by patient-related biological factors, at present it is still unknown whether the biological psychoendocrine and immune status of patients may also be important in conditioning the efficacy of cancer chemotherapy itself. The present study was carried out to investigate the influence of the endocrine immune and psychospiritual characteristics of patients on the efficacy of cancer chemotherapy for advanced neoplastic disease.

Patients and Methods

The study included 30 consecutive metastatic non-small cell lung cancer (NSCLC) patients who were admitted to the San Gerardo Hospital of Monza to receive chemotherapy for their neoplastic disease. Eligibility criteria were as follows: histologically proven metastatic NSCLC, measurable lesions, no double tumor, no brain metastasis, no previous chemotherapy for the metastatic disease, no chronic concomitant therapy with drugs influencing the immune and the endocrine systems (namely opioids and corticosteroids), no important medical illnesses other than cancer and in particular no concomitant endocrine or immune diseases. The clinical characteristics of patients are reported in Table I. Chemotherapy consisted of *i.v.* cisplatin at 30 mg/m²/day for 3 consecutive days plus gemcitabine at 1000 mg/m² at days 1 and 8, corresponding to one complete chemotherapeutic cycle. Cycles were repeated at 21-day intervals. Radiological examinations, including CT scan, NMR and/or PET, were made before and after 3 cycles of chemotherapy. The clinical response was evaluated according to WHO criteria. To evaluate lymphocyte number, venous blood samples were collected in the morning after an overnight fast before the onset of chemotherapy and every 21 days before the next chemotherapeutic cycle. The lymphocyte count was considered to be abnormally low when below 1500/mm³. The cortisol circadian rhythm was investigated by collecting serum samples before the start of chemotherapy at 8.00 a.m. and at 4.00 p.m. Cortisol secretion was investigated either before chemotherapy, or after 3 cycles of chemotherapy. Cortisol serum concentrations were measured by automated ECLA method (Modular Analytics E170, Roche Diagnostic GmbH, D-68298 Mannheim). Morning cortisol values for the healthy subjects (95% confidence limits) (12), were below 220 ng/ml, whereas in the afternoon the concentrations were lower at least than 30% with respect to those observed at 8.00 a.m. The psychological profile was analyzed using the Rorschach test (13); in particular, the presence of a normal sexual identity was taken into consideration within the great number of variables explored by the test, as shown in previous studies (14). Finally, as previously reported in the literature (15) and reported in Table II, the spiritual status was investigated by a specific clinical test for spirituality, consisting of 10 questions concerning the relationships between God, humans and world. The control group consisted of 100 age- and sex-matched healthy volunteers. The

Table I. *Clinical characteristics of 30 metastatic non-small cell lung cancer patients.*

Characteristics	n
M/F	26/4
Median age (years)	72 (49-79)
Median performance status (Karnofsky's score)	90 (70-100)
Tumor histotype	
Epidermoid carcinoma	10
Adenocarcinoma	14
Large cell carcinoma	6
Dominant metastatic site	
Soft tissues	9
Bone	1
Lung	17
Liver	1
Lung + Liver	1
Seroses	1

clinical results were analyzed by the Chi-square test, Student's *t*-test, analysis of variance and coefficient of correlation between lymphocyte count and cortisol concentration, as appropriate.

Results

A complete response (CR) occurred in 2/30 (7%) patients. A partial response (PR) was achieved in 9/30 (30%) patients. The number of objective tumor regressions was 11/30 (37%). Stable disease (SD) was found in 9/30 (30%) patients, with consequent disease-control (DC) of 20/30 (67%), whereas the remaining 10 (33%) patients had a progressive disease (PD). Table III shows the percentage of patients with normal or altered cortisol rhythm, lymphocyte count prior to therapy and response to the Rorschach test. Table IV shows the lymphocyte number before the onset of chemotherapy in relation to the other psychobiological variables. The mean number of lymphocytes observed in patients with normal cortisol secretion was significantly higher with respect to that found in those with anomalous cortisol production ($p < 0.05$). The lymphocyte mean number was also significantly higher in patients with normal identity according to the Rorschach test than in those with a loss of identity ($p < 0.025$). Finally, the lymphocyte count was higher in patients with a spiritual score greater than 65% than in those with values lower than 65%, without, however, statistically significant differences. In any case, no statistically significant correlation was found between lymphocyte count and morning cortisol concentrations ($r = -0.27$). The relationships between the clinical response to chemotherapy and the various psychobiological variables are reported in Table V. The percentage of objective tumor regressions (CR

Table II. *Clinical test for spirituality.*

N	Questions	Possible responses	Points
1	What do the commandments relate to:	a) the relationship with God b) the relationship between men c) I don't have a direct relationship with them	10 5 0
2	With the word "love" you associate:	a) God b) romanticism c) your partner	10 5 0
3	If you had to build a ladder of values, would you put on top:	a) praise God, love your neighbour b) have a family, work with success c) fulfil yourself socially and economically	10 5 0
4	Which word describes better the role of your father?	a) an image of God b) a guide c) a master	5 2.5 0
	Which word describes better the role of your mother?	a) an image of God b) a friend c) a rival	5 2.5 0
5	Which sentence best describes the word "regret"?	a) a misdeed towards God b) a feeling of hurt for the misdeeds you committed c) the violation of an ethical principle	10 5 0
6	In your opinion, sexual pleasure and mystical ecstasy...	a) are of the same nature b) are two completely different pleasures c) sex is an impulse, while mystical ecstasy concerns religion	10 5 0
7	How often are you happy for someone else's joy?	a) often b) seldom c) never	10 5 0
8	In your opinion, the sense of guilt depends ...	a) on the moral of a culture b) on human nature c) on the violation of a law	10 5 0
9	If the person with whom you are falling in love, already has another relationship, how would you behave?	a) hope that the person will receive the love that you would have given to her/him b) try to forget the person c) hope that the two will separate	10 5 0
10	If you are successful socially and economically, you would consider it...	a) a reason to thank God b) a fruit of your own commitment c) the wish of God	10 5 0

Table III. *Psychoimmunobiological characteristics of 30 metastatic cell lung cancer patients.*

Characteristics	n (%)
Cortisol circadian secretion	
Normal	17 (57%)
Altered	13 (43%)
Pre-treatment lymphocyte count	
Normal	18 (60%)
Lymphocytopenia (below 1500/mm ³)	12 (40%)
Rorschach test	
Normal identity	16 (53%)
Lack of identity	14 (47%)

Table IV. *Pretreatment lymphocyte number ($\bar{X} \pm SE$) in relation to the main biopsychospiritual variables.*

Characteristics	Lymphocytes (n/mm ³)
Cortisol circadian rhythm	
Normal	1986±123*
Altered	1461±97
Profile (Rorschach test)	
Presence of identity	1966±115
Lack of identity	1335±128**
Spiritual score	
Above 65%	1815±156
Below 65%	1554±138

* $p < 0.05$ vs. altered cortisol secretion; ** $p < 0.025$ vs. normal test (presence of identity).

Table V. Clinical response to chemotherapy (WHO criteria) in 30 metastatic non-small cell lung cancer patients in relation to pretreatment lymphocyte count, cortisol circadian rhythm, psychomental profile (Rorschach test) and spiritual score.

Characteristics	Clinical response (CR + PR)
Pretreatment lymphocyte count	
Normal	9/18 (50%)**
Lymphocytopenia (less than 1500/mm ³)	2/12 (17%)
Cortisol circadian rhythm	
Normal	9/17 (53%***)
Altered	2/13 (15%)
Profile (Rorschach test)	
Presence of identity	8/16 (50%)*
Lack of identity	3/14 (21%)
Spiritual score	
Above 65%	7/12 (58%***)
Below 65%	4/18 (22%)

* $p < 0.05$ vs. lack of identity; ** $p < 0.025$ vs. lymphocytopenic patients; *** $p < 0.01$ vs. below 65%, $p < 0.01$ vs. altered cortisol secretion; CR: complete response; PR: partial response.

+ PR) achieved in patients with a normal lymphocyte count was significantly higher than that obtained in patients with pre-treatment lymphocytopenia ($p < 0.025$). In the same way, the tumor regression rate observed in patients with a normal cortisol secretion was significantly higher than that found in those with anomalous cortisol circadian secretion ($p < 0.01$). On the other hand, as far as the relation between the efficacy of chemotherapy and psychospiritual status is concerned, the tumor response rate was significantly higher in patients with a normal identity according to the Rorschach test than in those with a loss of identity ($p < 0.05$) and in those with a spiritual score greater than 65% than in patients with values lower than 65% ($p < 0.01$). Table VI shows the mean values of the spiritual score in relation to the other clinical variables. The mean values of the spiritual score observed in cancer patients were lower than those found in the healthy volunteers, even though the difference did not reach statistical significance. The spiritual score was higher in responder patients than in those who had no tumor regression under chemotherapy, in patients with normal circadian cortisol secretion than in those with altered cortisol production, and in those with normal pretreatment lymphocyte counts than in patients with lymphocytopenia prior to therapy, but none of these differences was statistically significant. On the contrary, the mean values of the spiritual score observed in patients with a presence of identity according to the Rorschach test were significantly higher than in those with a loss of identity ($p < 0.05$). The variations in the cortisol rhythm and in lymphocyte number during cancer chemotherapy in relation

Table VI. Mean ($\bar{X} \pm SE$) values of the spiritual score in 30 metastatic non-small cell lung cancer patients in relation to response to chemotherapy, cortisol circadian rhythm, pretreatment lymphocyte count and profile (Rorschach test) and in 100 healthy volunteers as a control group.

Controls and patients	n	Spiritual score ($\bar{X} \pm SE$)
Healthy controls	100	68±2
Overall patients	30	58±4
Response to chemotherapy		
Responders (CR + PR)	11	63±5
Non-responders	19	56±4
Cortisol circadian rhythm		
Normal	17	64±3
Altered	13	54±6
Pretreatment lymphocyte number		
Normal	18	61±4
Lymphocytopenia (less than 1500/mm ³)	12	57±5
Profile to Rorschach test		
Presence of identity	16	68±3*
Lack of identity	14	51±4

* $p < 0.05$ vs. lack of identity; CR: complete response; PR: partial response.

to the clinical response are illustrated in Figures 1 and 2, respectively. Both morning and afternoon pre-treatment mean concentrations of cortisol observed in patients who had a PD were significantly higher than those observed in responder patients (morning: $p < 0.05$; afternoon: $p < 0.005$). Afternoon cortisol levels were also higher in progressing patients than in those with SD, even though the difference was statistically significant only for afternoon levels ($p < 0.05$), whereas no significant difference was found in the morning values. Both morning and afternoon cortisol concentrations decreased with therapy in responder patients and in those with SD, whereas they increased in progressing patients, although none of these differences was statistically significant. In more detail, an altered cortisol secretion prior to chemotherapy was present in 8/10 (80%) progressing patients, and in only 2/11 (18%) responder patients, and in 3/9 (33%) patients with SD. These differences were statistically significant ($p < 0.01$ vs. responder patients; $p < 0.05$ vs. patients with SD). Chemotherapy was followed by a normalization of the cortisol circadian rhythm in 2/2 patients who obtained tumor regression, in 1/3 patients with SD and in only 1/8 patients who had PD. The lymphocyte count progressively rose in responder patients and decreased in progressing patients, whereas it remained substantially unchanged in patients with SD, but none of these differences was statistically significant with respect to the baseline lymphocyte values prior to chemotherapy. The pre-treatment mean lymphocyte number observed in

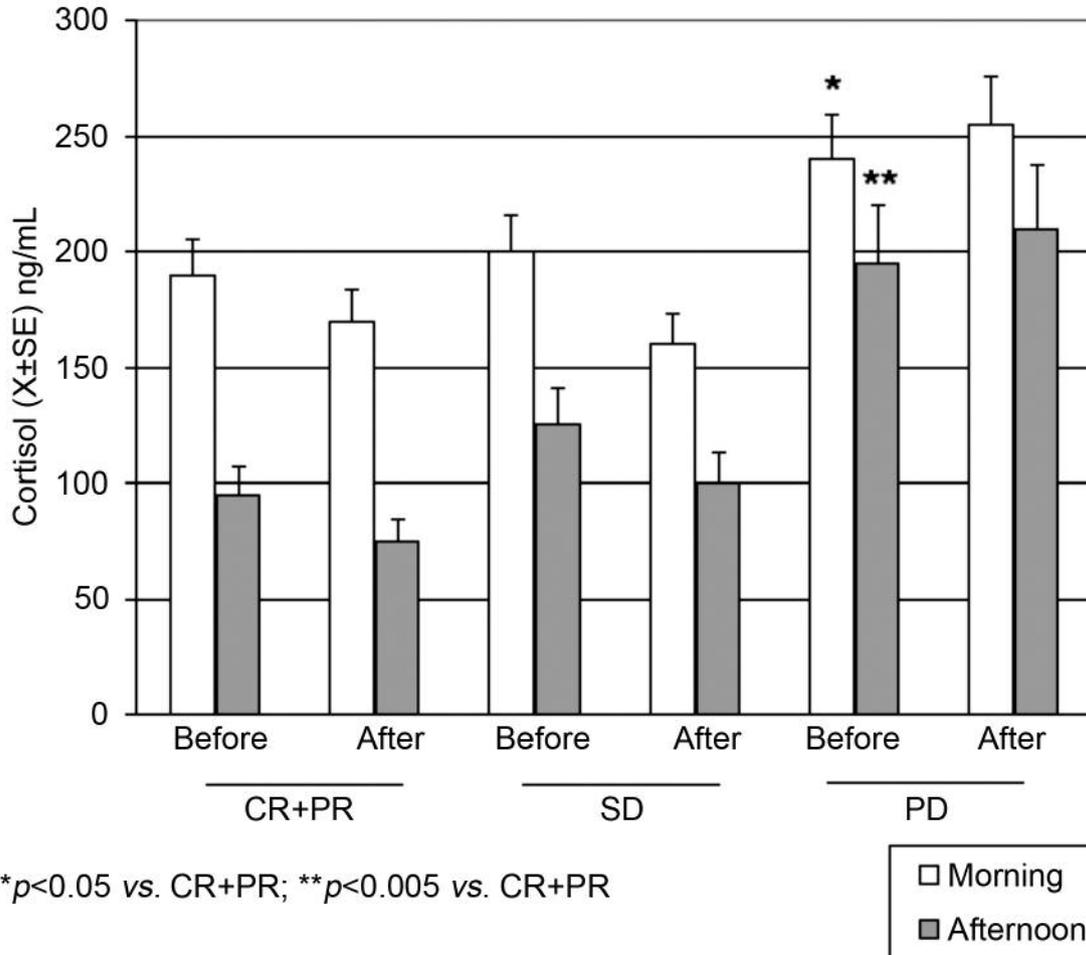


Figure 1. Circadian cortisol secretion before and after chemotherapy in lung cancer patients with complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

progressing patients was significantly lower than that shown by the responder patients ($p < 0.05$). It was also lower than that found in patients with SD, but the difference was not significant. Finally, the mean lymphocyte number during the whole period of chemotherapy was constantly significantly higher in responder patients than in those who had PD ($p < 0.025$ at day 21 and $p < 0.005$ at days 42 and 63).

Discussion

This preliminary study shows that the immune and neuroendocrine status of cancer patients may be influenced by their psychospiritual characteristics, as documented by the evidence of the most frequent presence of desynchronization in the cortisol circadian rhythm and of lymphocytopenia in patients with disturbances of their psychosexual identity and of their spiritual life. Since the neuroimmune system is physiologically under psychoemotional and spiritual

modulation (16), it is probable that both alterations of the cortisol secretion and decline in lymphocyte number, with a subsequent diminished anticancer immune reactivity, may simply represent the biological expression of the progressive loss of the psychospiritual identity and of the significance of life. Moreover, this study would suggest that the efficacy of cancer chemotherapy itself, at least in lung cancer patients, may depend not only on tumor characteristics, but also on the psychospiritual status of the individual patient by influencing the immune and neuroendocrine functions, which plays a fundamental role in the control of neoplastic growth (1-5). In particular, it should be considered that the alterations of cortisol secretion do not represent a simple metabolic or analytical anomaly, but might constitute a clinical sign of biological desynchronization, since they would reflect a separation between the single human biopsychological identity and the universal environmental informations. To date, the relation between cancer chemotherapy and the psychological profile was investigated

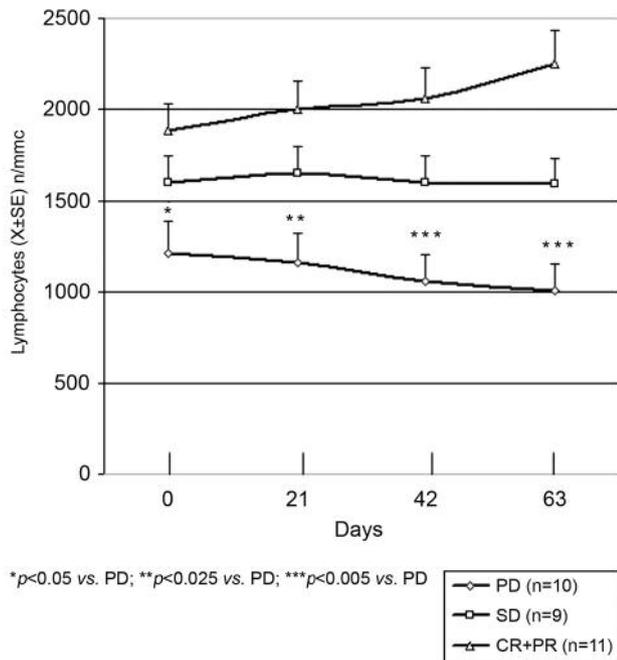


Figure 2. Lymphocyte mean number during cancer chemotherapy in lung cancer patients with complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

only in terms of psychological acceptance and tolerability. The present study represents the first clinical evidence showing that the efficacy of chemotherapy may also be influenced by the neuroimmune and the psychospiritual conditions of cancer patients. This evidence is not surprising if we take into consideration the recently demonstrated modulatory effect of cancer chemotherapy on the cytokine network (17). Since the cytokines released from the activated immune cells may exert also endocrine effects (18), chemotherapy-induced changes in the endogenous secretion of cytokines may allow concomitant variations in endocrine functions, including that of the cortisol rhythm, as confirmed by the normalization of a previously altered cortisol circadian secretion in cancer patients, who achieved a tumor regression in response to cancer chemotherapy. In conclusion, the following statements seem to be justified from the present study: i) the evidence of lymphocytopenia and/or an altered cortisol circadian rhythm prior to chemotherapy may predict a lack of therapeutic efficacy; ii) the efficacy of chemotherapy is associated with an improvement in the immune neuroendocrine status of cancer patients, with an increase in lymphocyte number and possible normalization of neuroendocrine alterations, such as the disturbances of the cortisol circadian rhythm.

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Received October 12, 2007
 Revised December 21, 2007
 Accepted February 20, 2008