

A Spiritual Approach in the Treatment of Cancer: Relation between Faith Score and Response to Chemotherapy in Advanced Non-small Cell Lung Cancer Patients

P. LISSONI¹, G. MESSINA¹, D. PAROLINI¹, A. BALESTRA¹, F. BRIVIO²,
L. FUMAGALLI², L. VIGORE³ and F. ROVELLI³

Divisions of ¹Radiation Oncology and ²Surgery and
³Laboratory of Immunobiology, San Gerardo Hospital, Monza, Milan, Italy

Abstract. *Background:* The recent advances in the psycho-oncological and psychoneuroimmunological investigations of cancer patients has allowed the rediscovery of the importance of spiritual faith in influencing the clinical course of neoplastic disease, not only in terms of supportive care but also as a potential prognostic variable. *Materials and Methods:* Clinical criteria were worked out to explore the existence of a real status of faith, in an attempt to correlate the degree of faith 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. *Results:* The tumor response rate achieved in patients with a high degree of faith was significantly higher than in the other group of patients. Moreover, the mean postchemotherapeutic lymphocyte number was significantly higher in the patients with evident spiritual faith than in the other patients. Finally, the percent age of 3-year survival observed in the patients with a high degree of faith was significantly higher than that in the patients with a low faith score. *Conclusion:* This preliminary study suggests that spiritual faith may positively influence the efficacy of chemotherapy and the clinical course of neoplastic disease, at least in lung cancer, by improving the lymphocyte-mediated anticancer immune response.

Until a few years ago, it was unusual to include simple psychological supportive care within the technical interventions for treating cancer. Now, as a result of discoveries in the psychoimmunobiology of cancer (1-3), it is fundamental to take into consideration not only the

psychological status of patients, but also the spiritual aspect of human life (4). Most authors still tend to consider spirituality simply as a part of psychological behaviour (5), but recently some investigators have suggested that spirituality is a reality rather than just a psychological phenomenon (6, 7). Moreover, there is no agreement in the interpretation of the terms religion and spirituality, which have been considered as either the same or different conditions (5-7). Recently, the National Cancer Institute proposed an adequate definition of religion as a set of beliefs and practices associated with a religion and spirituality as the search for the ultimate meaning of life through religion itself or other mystical ways (8).

At present, the main problem for realizing not only the simple application of spiritual techniques as support care in cancer, but also effective clinical spirituality, is represented by the need to identify which blood biochemical parameters, if any, may reflect the psychological and spiritual characteristics of an individual cancer patient. This statement is justified by recent studies suggesting that spiritual support may allow an increase in the survival time of advanced cancer patients (5, 9). However, little is known about how spiritual support may influence the clinical course of neoplastic disease, even though some preliminary studies would suggest that a high spiritual status may counteract cancer growth by stimulating the anticancer immune responses (10), which are mainly mediated by lymphocytes (11). In addition, recent discoveries in the area of the psychoneuroendocrinology (PNEI) have demonstrated that the *in vivo* immune response, including anticancer immunity, is under physiological modulation exerted by the neuroendocrine system (1-3), mainly by the pineal gland, brain, opioid system and endocannabinergic system (12-14). It is therefore probable that possible biochemical markers of psychospiritual status could be identified within the psychoneuroimmune functions.

In particular, it has been shown that the presence of a normal cortisol circadian rhythm may be considered as a sign of the maintenance of physiological synchronization between the

Correspondence to: Dr. Paolo Lissoni, Divisione di Radioterapia Oncologica, Ospedale S. Gerardo, 20052 Monza, Milano, Italia. Fax: +39 0392332284, e-mail: p.lissoni@hsgerardo.org

Key Words: Cancer chemotherapy, faith, immunity, lung cancer, spirituality.

Table I. *The major criteria for a high faith score in advanced cancer patients.*

1	Adequate and conscious knowledge of diagnosis and prognosis of disease.
2	No excessive anxiety.
3	Lack of an excessive analytical tendency to understand the mechanisms of the efficacy of the treatments and disease progression.
4	No illusions regarding the professional ability of the clinicians.
5	Perception of the disease not only as a personal problem, but as a sign of the suffering human condition.

surroundings overall and the biological rhythms of a patients (15). Moreover, it has been demonstrated that evidence of normal cortisol circadian secretion is generally associated with the concomitant presence of a normal light/dark rhythm of the pineal hormone melatonin (16), which plays a fundamental role in the psychoneuroimmunomodulation of immune responses and of tumor onset and development (13). Finally, the presence of normal cortisol circadian secretion has been proven to be associated with a better prognosis in cancer patients with advanced disease (17, 18). Only when the biochemical neuroendocrine and immune markers of psychospiritual status are identified will it become possible to transform the spiritual approach in the treatment of cancer from simple supportive care into a therapeutic strategy to modify the prognosis by influencing host–tumor interactions. In fact, it is known that the prognosis of neoplastic disease is progressively more unfavourable concomitant to the severity and frequency of the endocrine, neuroendocrine and immune alterations occurring in cancer patients (15). It should be noted that spiritual faith is not simply religious belief, but is primarily a state of consciousness which adheres to an ideal code of belief / rule of life without having a subjective experience or confirmation (7-11).

Unfortunately, from a clinical point of view, most clinical questionnaires developed to investigate the spiritual needs of patients are limited to the analysis of the external behaviour of patients, in particular the participation in some religious community, without exploring the real psychospiritual dimension (5-10). One of the most suitable questionnaires to assess spiritual life is that suggested by the FICA (faith, importance, community, action in care) criteria (19), which analyzes the four main parameters through specific questions.

Our previous studies have already suggested the possibility of achieving a greater efficacy of chemotherapy and longer survival in metastatic cancer patients in the presence of a spiritual feeling, as assessed by evaluating the answers to a special patient report (20). Subsequently, we also identified five major criteria for the clinical evaluation of the status of faith by medical oncologists during their contact with cancer patients, as reported in Table I. These quantification criteria have been standardized on the basis of our long experience in medical oncology and critical analysis of the points of view of other authors involved in this area of spirituality (5-10). By using these criteria, the clinical response to chemotherapy

and the survival time in relation to the patient score of faith were analyzed in this study. Non-small cell lung cancer (NSCLC) was chosen as the tumor histotype on the basis of our previous psychoncological investigations, which have suggested that lung cancer patients are those in whom the influence of the psychospiritual status on the prognosis of disease is more evident (4, 20).

Patients and Methods

The study included 50 consecutive patients suffering from metastatic NSCLC. 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 concomitant 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 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 was planned, consisting of a weekly low-dose of taxotere, followed by supportive care alone. The clinical characteristics of the patients are reported in Table II.

The clinical approach to investigate the spiritual faith consisted of the evaluation of the five major criteria as shown in Table I. 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, since if the very bad prognosis of their disease is not known, an eventual apparent designation of faith would simply be an emotional illusion. High faith status is the opposite of anxiety, so clinical evidence of exaggerated anxiety would exclude a real status of faith. The intellectual knowledge of the mechanisms of action of cancer chemotherapy and those responsible for cancer progression does not obviously enhance the efficacy of the chemotherapy itself, so an excessive analytical tendency would also exclude a real status of faith, by simply representing 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 real status of faith. Finally, since the most evident effect of a real spiritual faith is the perception of the unity of life, with the amplification of spiritual sensitivity, the perception of the patient's own disease as being the only problem,

Table II. Clinical characteristics of 50 metastatic non-small cell lung cancer patients according to faith score (FS).

Characteristics	FS \geq 60%	FS <60%
No. patients	24	26
Male/female	18/6	17/9
Median performance status (Karnofsky's score)	90 (80-100)	90 (80-100)
Histotypes		
Epidermoid carcinoma	8	9
Adenocarcinoma	13	14
Large cell carcinoma	3	3
Dominant metastasis sites		
Nodes	2	3
Bone	3	4
Lung	14	13
Liver	4	4
Lung + liver	1	2

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 60 (60%).

The clinical response to chemotherapy was assessed by the WHO criteria. To evaluate the changes in lymphocyte count, venous blood samples were collected in the morning after an overnight fast before the onset of chemotherapy and at weekly intervals until 1 month after the last chemotherapeutic injection. The data were statistically analyzed by the Chi-square test, Student's *t*-test and analysis of variance, as appropriate. The patients were followed up for a minimum of 36 months. The 3-year survival curves were plotted according to the Kaplan-Meier method and statistically analyzed by the log-rank test.

Results

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 clinical characteristics of the two groups of patients with faith scores of less or greater than 60% are reported in Table II. 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 percent age of patients with faith scores greater than 60% (18/35 (51%) vs. 6/15(40%)).

The overall clinical response to chemotherapy is reported in Table III. The clinical response to cancer chemotherapy in relation to the score of faith is reported in Table IV. The tumor response rate (CR+PR) achieved in the patients with a faith score equal to or greater than 60% was significantly higher than that found in the patients with a faith score less

Table III. Clinical response (WHO criteria) to chemotherapy of cisplatin plus gemcitabine in 50 metastatic non-small cell lung cancer patients.

Clinical response n (%)				
CR	PR	CR+PR	SD	PD
6 (12%)	9 (18%)	15 (30%)	18 (36%)	17 (34%)

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table IV. Clinical response to cancer chemotherapy in relation to the faith score.

Faith score %	n	Clinical response				
		CR	PR	CR+PR	SD	PD
<60%	26	1 (4%)	3 (12%)	4 (16%)	10 (38%)	12 (46%)
\geq 60%	24	5 (21%)	6 (25%)	11 (46%)*	7 (29%)	6 (25%)

CR: complete response; PR:partial response; SD: stable disease; PD: progressive disease; * $p<0.01$ vs. faith score <60% .

Table V. Faith score (mean \pm SE) in relation to the clinical response to cancer chemotherapy.

Faith score %	Clinical response				
	CR	PR	CR + PR	SD	PD
	83 \pm 5	71 \pm 4	76 \pm 4 *	52 \pm 5	31 \pm 3

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

than 60% (11/24 (46%) vs. 4/26 (16%), $p<0.01$). Table V 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.

Figure 1 illustrates the mean lymphocyte 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 postchemotherapeutic 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 ($p<0.01$).

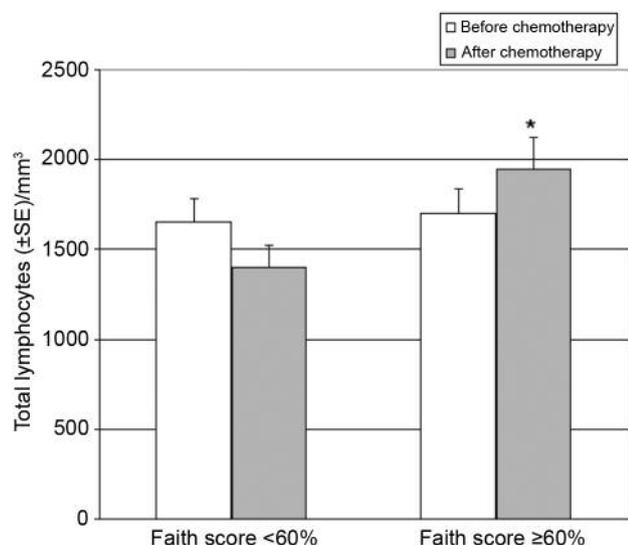


Figure 1. Mean lymphocyte number observed before and after chemotherapy (cisplatin + gemcitabine) in 50 metastatic non-small cell lung cancer patients with faith score above or below 60%. * $p < 0.01$ vs. Faith score <60%.

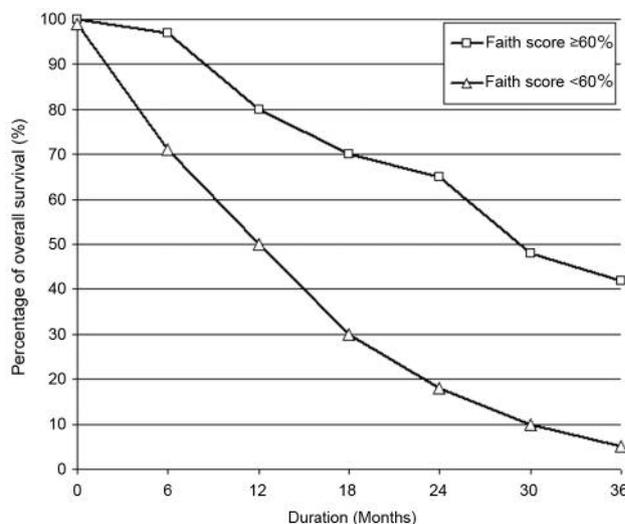


Figure 2. 3-Year survival curves achieved in metastatic non-small cell lung cancer patients in relation to their faith score. $p < 0.05$ for difference between survival curves.

Finally, Figure 2 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% ($p < 0.005$).

Discussion

The results of this preliminary study, performed on the basis of a clinical evaluation of the spiritual faith carried out by the physicians themselves, suggested that the evidence of a high degree of faith as an expression of an active spiritual life was associated with a greater efficacy of cancer chemotherapy and may predict a longer survival in metastatic cancer patients, at least in NSCLC. Since the chemotherapeutic regimen was the same in all the patients and the tumor histotypes and sites of metastases were similar in the groups of patients with a high or a low degree of faith, the difference in the efficacy of chemotherapy and in the survival times cannot be explained only in terms of tumor biological characteristics, but depended, at least in part, on the different psychospiritual status of the patients, as assessed by the specific faith score. However, further studies in a greater number of patients and by multivariate analysis will be necessary to confirm these data and to exclude the importance of possible other variables, such as different tumor oncogene expression. Moreover, this study showed that the greater efficacy of chemotherapy was associated with a postchemotherapeutic increase in total lymphocyte count, suggesting that the positive influence of the spiritual faith on the efficacy of cancer chemotherapy and on the prognosis of the disease in terms of overall survival time may be mediated at

least in part by activation of anticancer immunity, as already proposed by other authors, either in treated patients (21) or in those who had spontaneous tumor regression (22).

Even though spiritual faith cannot obviously be artificially quantified, the major criteria for spiritual faith suggested by this study seemed to be able to clinically investigate the psychospiritual condition of the patients, without need of questionnaires or other specific tests. In addition, it is obvious that the spiritual condition cannot directly influence the chemical action of the chemotherapeutic agents. Thus, it is probable that the modulation of anticancer immunity may represent one of the major mechanisms responsible for the positive prognostic influence of high spiritual status on the prognosis of cancer. Further studies, however, will be required to better define immune system–psychospiritual status interactions, at least by measuring the different lymphocyte subpopulations and the serum concentrations of the main cytokines involved in regulating the anticancer immunity, namely IL-2 (11). Previous clinical investigations have demonstrated that chemotherapy itself may influence the cytokine network (23), stimulating or suppressing the antitumor immune reaction, probably depending on the psychoneuroendocrine condition of the patients (20). Therefore, the positive influence of spiritual faith on the efficacy of cancer chemotherapy could be mediated at least in part by directing the action of chemotherapy on the cytokine network towards promoting antitumor activity.

If subsequent clinical studies in a greater number of patients and in patients with tumor histotypes other than NSCLC confirm the preliminary results of this study, the

clinical investigation of the spiritual status of patients and the application of psychospiritual techniques to cancer therapy could be routinely included in the clinical management of cancer patients suffering from an incurable neoplastic disease.

References

- 1 Rubinow DR: Brain, behaviour and immunity: an interactive system. *J Natl Cancer Inst Monogr* 10: 79-86, 1990.
- 2 Jankovic BD: Neuroimmunomodulation. *Ann NY Acad Sci* 741: 3-38, 1994.
- 3 Antoni MH: Psychoneuroimmunology of cancer. *Brain Behav Immun* 17: 84-91, 2003.
- 4 Messina G, Lissoni P, Bartolacelli E, Tancini G, Villa S, Gardani GS and Brivio F: A psychoncological study of lymphocyte subpopulations in relation to pleasure-related neurobiochemistry and sexual and spiritual profile to Rorschach's test in early or advanced cancer patients. *J Biol Regul Homeost Agents* 17: 322-326, 2003.
- 5 Balducci L and Meyer R: Spirituality and medicine: a proposal. *Cancer Con* 8: 368-376, 2001.
- 6 Chander E: Spirituality. *Hospice J* 14: 63-74, 1999.
- 7 Post SG, Puchalsky CM and Larson DB: Physicians and patient spirituality: professional boundaries, competency and ethics. *Ann Intern Med* 132: 578-583, 2000.
- 8 Balboni TA, Vanderwerker L, Block SD, Paulk ME, Lathan CS, Peteet JR and Prigerson HG: Religiousness and spiritual support among advanced cancer patients and associations with end-of-life treatment preferences and quality of life. *J Clin Oncol* 25: 555-560, 2007.
- 9 Sloan RP, Bagiella E and Powell T: Religion, spirituality and medicine. *Lancet* 353: 664-667, 1999.
- 10 De Marco DG: Medicine and spirituality. *Ann Intern Med* 133: 920-921, 2000.
- 11 Whittington R and Faulds D: Interleukin-2. *Drugs* 46: 446-483, 1993.
- 12 Lewis JW, Shavit Y, Terman GW, Nelson IR, Gale RP and Liebeskind JC: Apparent involvement of opioid peptides in stress-induced enhancement of tumor growth. *Peptides* 4: 635-638, 1983.
- 13 Maestroni GJM: The immunoneuroendocrine role of melatonin. *J Pineal Res* 14: 1-10, 1993.
- 14 Grotenhermen F: Pharmacology of cannabinoids. *Neuroendocrinol Lett* 25: 14-23, 2004.
- 15 Mormont MC and Levi F: Circadian system alterations during cancer progression: a review. *Int J Cancer* 70: 241-247, 1997.
- 16 Mazzoccoli G, Carughi S, De Cata A, La Viola M and Vendemiale G: Melatonin and cortisol serum levels in lung cancer patients at different stages of disease. *Med Sci Monit* 6: 11, 2005.
- 17 Sephton SE, Sapolsky RM, Kraemer HC and Spiegel D: Diurnal cortisol rhythm as a predictor of breast cancer survival. *J Natl Cancer Inst* 92: 994-1000, 2000.
- 18 Lissoni P, Brivio F, Fumagalli L, Messina G, Secreto G, Romelli B, Fumagalli G, Rovelli F, Colciago M and Brera G: Immune and endocrine mechanisms of advanced cancer-related hypercortisolemia. *In Vivo* 21: 647-650, 2007.
- 19 Ferrell B: Meeting spiritual needs: what is an oncologist to do? *J Clin Oncol* 25: 467-468, 2007.
- 20 Lissoni P, Messina G, Balestra A, Colciago M, Brivio F, Fumagalli L, Fumagalli G and Parolini D: Efficacy of cancer chemotherapy in relation to synchronization of cortisol rhythm, immune status and psycho spiritual profile in metastatic non-small cell lung cancer. *In Vivo*, 2008.
- 21 Berland W: Can the self affect the course of cancer? *Advances* 11: 5-19, 1995.
- 22 Kappauf H, Gailmeier WM, Wunsch PH, Mittelmeier HO, Birkmann J, Buschel G, Kaiser G and Kraus J: Complete spontaneous remission in a patient with metastatic non-small cell lung cancer. *Ann Oncol* 8: 1031-1039, 1997.
- 23 Ehrke MJ, Mihich E, Berd D and Mastrangelo MJ: Effects of anticancer drugs on the immune system. *Semin Oncol* 16: 230-239, 1989.

Received February 4, 2008

Revised May 2, 2008

Accepted May 9, 2008