Synchronization of Cortisol Circadian Rhythm by the Pineal Hormone Melatonin in Untreatable Metastatic Solid Tumor Patients and its Possibile Prognostic Significance on Tumor Progression

FERNANDO BRIVIO[1], LUCA FUMAGALLI[1], GABRIELE FUMAGALLI[2], SIMONETTA PESCIA[2], RINALDO BRIVIO[2], GIUSEPPE DI FEDE[3], FRANCO ROVELLI[2] and PAOLO LISSONI[3]

[1]*Surgical Division, Bassini Hospital, Cinisello Balsamo, Milan, Italy;*
[2]*Department of Clinical Pathology, S.Gerardo Hospital, Monza, Italy;*
[3]*Institute of Biological Medicine, Milan, Italy*

Abstract. *Background: Cancer progression has been associated with neuroendocrine alterations involved in the control of the circadian rhythms, particularly those of cortisol. Moreover, the evidence of an altered cortisol rhythm may predict a poor prognosis in cancer patients. Finally, cancer progression has been proven to be associated with alterations in the pineal gland, which plays a fundamental role in the control of circadian biological rhythms. On this basis, a study was planned to evaluate the effects of a chronic treatment with the pineal hormone melatonin (MLT) in advanced cancer patients with altered cortisol circadian rhythm. Patients and Methods: The study included 14 untreatable metastatic cancer patients showing alterations of cortisol rhythm. They were treated by MLT at 20 mg/day orally, in the evening, for 3 consecutive months. Results: a normalization of cortisol rhythm was achieved in 4/14 (29%) patients. Moreover, stable disease (SD) was obtained in 6/14 (43%) patients under MLT therapy, whereas the other 8 patients had progressive disease (PD). Finally, the percentage of cortisol rhythm normalization achieved in patients with SD was significantly higher than that observed in patients with PD. Conclusion: These results show that MLT may normalize cortisol rhythm in advanced cancer patients and this effect appears to be associated with SD, thus confirming the negative prognostic significance of cortisol rhythm alterations in cancer.*

Several authors have reported the occurrence of alterations in biological circadian rhythms with cancer progression (1-3), reflecting cancer-induced desynchronization of the biological activities. The evidence of alterations in circadian secretion of cortisol is one of the most frequent signs of cancer-related desynchronization (1-3). Moreover, it has been demonstrated that the evidence of an altered cortisol rhythm is not a simple epiphenomenon only, but it has been proven to be associated with cancer progression and with a consequent poor prognosis (4, 5). The association between cortisol rhythm alterations and tumor progression has been documented in both experimental (1) and clinical studies (6, 7). In addition, the evidence of a poor prognosis in the presence of an altered cortisol rhythm would depend on its association with either a more severe immunosuppressive status (8), or a deficient pineal endocrine function (9), whose antitumor activity has been well demonstrated (10). In any case, the pineal gland plays a fundamental physiological role in the regulation of the chronobiologiocal rhythms through its most known hormone, melatonin (MLT), and by interacting with the suprachiasmatic nucleon (11). The alterations of cortisol rhythm may depend at least in part on the well-documented cancer-related pineal damage with tumor progression (12). In fact, under experimental conditions, it has been shown that a chronic treatment with MLT may restore a normal cortisol circadianicity in tumor-bearing animals with an altered cortisol rhythm (13). On this basis, a study was planned to evaluate the influence of a chronic administration of MLT on cortisol rhythm alterations occurring in metastatic cancer patients who failed to respond to conventional anticancer therapies.

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

Key Words: Chronobiology, cortisol rhythm, melatonin, pineal gland, synchronization.

Patients and Methods

The study was carried out in a group of 14 untreatable metastatic cancer patients with evidence of alterations in cortisol rhythm and secretion. Eligibility criteria were as follows: histologically proven metastatic solid tumor, measurable lesions, lack of a physiological cortisol circadian rhythm, no brain metastases, no double tumor, no

Table I. *Clinical characteristics of 14 metastatic cancer patients treatet by melatonin.*

Characteristic	n
M/F	10/4
Median age (years)	67 (50-76)
Tumor histotypes	
Non-small cell lung cancer	5
Pancreatic adenocarcinoma	4
Prostate cancer	3
Malignant melanoma	2
Dominant metastasis sites	
Nodes	2
Bone	2
Lung	3
Liver	5
Liver + lung	1
Peritoneum	1

availability of further anticancer standard therapies and no concomitant chronic therapies with drugs influencing cortisol secretion, including corticosteroids and opioid agents. Alteration of cortisol rhythm was defined as the absence of the physiological decline of cortisol levels during the afternoon greater by at least 30% with respect to the values observed in the morning. The clinical characteristics of patients are reported in Table I. According to previous clinical studies (14, 15), MLT was given orally at pharmacological doses consisting of 20 mg/day in the evening every day without interruption for at least 3 consecutive months. The experimental protocol was explained to each patient and informed consent was obtained. To evaluate cortisol circadian rhythm, venous blood samples were collected at 8.00 A.M. and at 4.00 P.M. either before the onset of MLT treatment, or after 3 months of MLT administration. Serum levels of cortisol were measured in duplicate by an automated analyser with an ECLIA method (Elecsys Systems Immunoassay; Roche Diagnostics, Mannheim, Germany). The clinical response was evaluated according to WHO criteria by repeating the radiological investigations after 3 months of treatment. Data were statistically analyzed by the chi-square test, the Student's *t*-test and the analysis of variance, as appropriate.

Results

A normalization of cortisol rhythm, with a decline greater than 30% in its levels during the afternoon was achieved after chronic administration of MLT in 4/14 (29%) patients. As far as the clinical response is concerned, no complete or partial tumor regression was found. However, stable disease (SD) was achieved in 6/14 (43%), with a median duration of 9 months (range 4-14 months), whereas the remaining 8 (57%) patients had a progressive disease (PD). In patients with SD, MLT treatment was continued without interruption until disease progression. In addition, by considering the changes of cortisol circadianicity in relation to the clinical response, a normalization of cortisol rhythm was obtained in

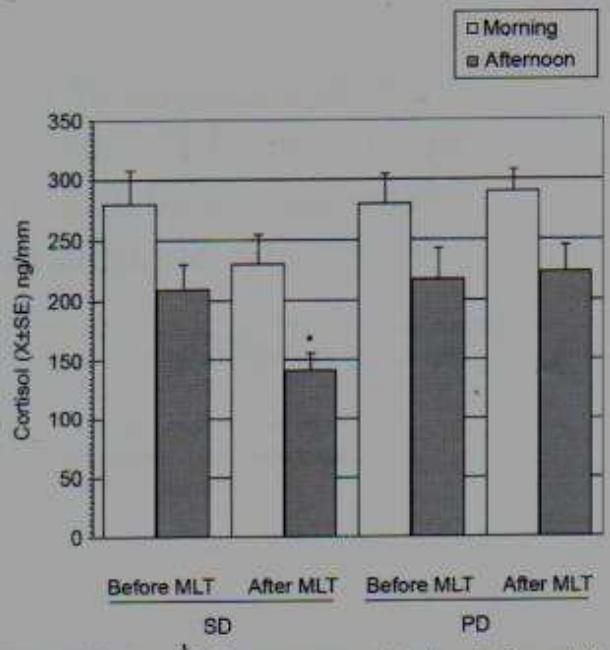

Figure 1. *Morning and afternoon mean cortisol values, before and after MLT therapy in cancer patients with stable (SD) and progressive (PD) disease. *p<0.025 vs. afternoon value before therapy.*

4/6 (67%) patients with SD and in none of the patients with PD. Then, the percentage of cortisol rhythm normalization obtained in patients with SD was significantly higher with respect to that observed in patients with PD in response to MLT administration ($p<0.01$). Changes in serum (mean±SE) morning and afternoon levels of cortisol observed before and after MLT therapy are illustrated in Figure 1. No significant difference in either morning or afternoon cortisol mean concentrations was seen before treatment between patients with PD or SD. Moreover, no significant variation in both morning and afternoon cortisol mean levels was observed in patients with PD after MLT therapy with respect to the values seen prior to treatment. On the contrary, in patients who achieved SD, mean afternoon concentrations of cortisol significantly diminished after MLT therapy ($p<0.025$). Morning mean cortisol values also decreased after MLT therapy, without, however, statistically significant differences. No MLT-related toxicity occurred. On the contrary, most patients referred to a relief of anxiety and an improvement in asthenia and well-being. In addition, no cachectic weight loss occurred under MLT administration.

Discussion

According to previous clinical investigations, the pineal hormone MLT is able alone to induce control of the neoplasic growth in a considerable number of advanced cancer patients for whom no other standard therapy was

available (14, 15). Moreover, as previously demonstrated in animals (13), even though the limited number of patients does not allow us to draw definite conclusions, this study would represent the first human evidence showing that chronic treatment with MLT may restore a normal cortisol circadian rhythm in advanced cancer patients with an altered psychoneuroendocrine function, and with a consequent altered cortisol secretion. Since the alteration of cortisol rhythm may be considered as the most typical sign of desynchronization of a living organism, the normalization of cortisol circadianicity by MLT would demonstrate the importance of the pineal gland in determining and maintaining the status of synchronization also in humans. Moreover, the frequent control of neoplastic growth in those patients who responded with a normalization of cortisol rhythm to MLT therapy would suggest that induction of a normal cortisol secretion may be involved at least in part in determining MLT-related inhibition of cancer progression. Therefore, MLT could be successfully used in the treatment of oncologic patients to correct cancer-related desynchronization of the biological circadian rhythms, namely of cortisol itself.

References

1 Mormont MC and Levi F: Circadian system alterations during cancer progression: a review. Int J C The pineal gland and cancer *70*: 241-247, 1997.

2 Touitou Y, Bogadan A, Levi F, Benavides M and Auzeby A: Disruption of the circadian patterns of serum cortisol in breast and ovarian cancer patients: relationships with tumour marker antigens. Br J Cancer *74*: 1248-1252, 1996.

3 Van der Pompe G, Antoni MH and Heijnen CJ: Elevated basal cortisol levels and attenuated ACTH and cortisol response to a behavioural challenge in women with metastatic breast cancer. Psychoneuroendocrinology *21*: 361-374, 1996.

4 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.

5 Lissoni P, Brivio F, Fumagalli L, Messina G, Secreto G, Romell B, Fumagalli G, Rovelli F, Colciago M and Brera G: Immuna and endocrine mechanisms of advanced cancer-relatec hypercortisolemia. In Vivo *21(4)*: 647-650, 2007.

6 McEwen BS, Biron CA, Brunson KW, Bulloch K, Chanber WH, Dhabhar FS, Goldfarb RH, Kitson RP, Miller AH, Spence RL and Wiess JM: The role of adrenocorticoids as modulator of immune function in health and disease: neural, endocrine an immune interactions. Brain Res Rev *23*: 79-133, 1997.

7 Antoni MH: Psychoneuroimmunology of cancer. Brain Beha Immun *17*: 84-91, 2003.

8 Lissoni P, Messina G, Parolini D, Balestra A, Brivio F, Fumagall L, Vigoré L and Rovelli F: A spiritual approach in the treatmen of cancer: relation between faith score and response t chemotherapy in advanced non-small cell lung cancer patients In Vivo *22*: 577-582, 2008.

9 Mazzoccoli G, Carughi S, De Cata A, La Viola M an Vendemiale G: Melatonin and cortisol serum levels in lun cancer patients at different stages of disease. Med Sci Monit 6 11-13, 2005.

10 Maestroni GJM: The immunoneuroendocrine role of melatonin J Pineal Res *14*: 1-10, 1993.

11 Brzezinski A: Melatonin in humans. N Engl J Med *336*: 186 195, 1997.

12 Bartsch C, Bartsch H and Lippert TH: The pineal gland an cancer: facts, hypotheses and perspectives. Cancer J 5: 194-199 1992.

13 Otalora BB, Madrid JA, Alvarez N, Vicente V and Rol MA Effects of exogenous melatonin and circadian synchronizatio on tumor progression in melanoma-bearing C57BL6 mice J Pineal Res *44*: 307-315, 2008.

14 Conti A and Maestroni GJM: The clinical neuroimmunotherapeuti role of melatonin in oncology. J Pineal Res *19*: 103-110, 2001.

15 Lissoni P: Is there a role for melatonin in supportive care? Supp Care Cancer *10*: 110-116, 2002.

Received October 15, 200

Accepted February 17, 201