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Original Paper

Is There a Role for Melatonin in the Treatment of Neoplastic Cachexia?

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It is known that neoplastic cachexia shows metabolic characteristics different from other common causes of malnutrition, and that it is mainly due to an abnormal secretion of TNF, whose levels are often high in patients with advanced neoplasia. Previous clinical studies have suggested that the pineal hormone melatonin (MLT), which plays an essential role in the neuroendocrine regulation of biological systems, may improve the clinical status of advanced cancer patients and inhibit TNF secretion. To investigate the relationship between MLT, TNF and cancer-related weight loss, 100 untreatable metastatic solid tumour patients entered this study to receive either supportive care alone, or supportive care plus MLT (20 mg/day orally in the evening). Patients were observed for 3 months, and were considered evaluable when they were observed for at least 2 months. There were 86 evaluable patients, the other 14 patients having died from rapid progression of disease. The per cent of weight loss greater than 10% was significantly higher in patients treated by supportive care alone than in those concomitantly treated by MLT, with no difference in food intake ($P < 0.01$). Mean serum levels of TNF progressively increased in the supportive care group, but to levels that were not significantly different from pretreatment values. In contrast, TNF mean concentrations significantly decreased ($P < 0.05$) in patients concomitantly treated by MLT. These results suggest that the pineal hormone MLT may be effective in the treatment of the neoplastic cachexia by decreasing TNF blood concentrations.

Key words: melatonin, neoplastic cachexia, tumour necrosis factor-alpha
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INTRODUCTION

It is known that cachexia is one of the most frequent paraneoplastic manifestations in advanced cancer [1]. About one-third of cancer patients may present weight loss [1]. No correlation between cachexia and type or site of cancer has been documented [2]. Obviously, weight loss and cachexia may be caused by the toxicity of antitumour therapies, decreased caloric intake, malabsorption, loss of material from the body and changes in body metabolism [1, 2]. However, several experiments have demonstrated that malnutrition alone cannot explain the neoplastic cachexia [1]. In addition, weight loss associated with neoplastic cachexia shows particular characteristics with respect to other types of weight loss, such as those related to starvation. In non-neoplastic subjects with starvation, the caloric expenditure is lowered, amino acids are used for gluconeogenesis and exogenous glucose is promptly oxidised. In contrast, in neoplastic cachexia, the caloric expenditure remains high and the basal metabolic rate is increased [1].

Recent clinical and biological studies have demonstrated that the neoplastic cachexia may depend on alterations of both endocrine and cytokine secretions. With regard to endocrine anomalies, it has been observed that neoplastic cachexia is often associated with a lack of a physiological decline in triiodothyronine (T3) levels, the so-called only low T3 syndrome, which has been shown to occur in the presence of severe clinical conditions [3]. Even though there are contro-

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versial data [4], preliminary results would suggest that neoplastic cachexia depends, at least in part, on enhanced production of tumour necrosis factor-alpha (TNF) [5], which appears to induce either antitumour immunological effects, or important metabolic side-effects, including cachexia. The blood concentrations of TNF are often abnormally elevated in cancer patients, mainly in those with disseminated disease [6, 7]. The mechanisms responsible for enhanced TNF secretion in advanced neoplasia are still unknown. In normal physiological conditions, TNF secretion is regulated by interleukin-2 (IL-2) [4, 5], released by T helper-type 1 lymphocytes (TH1). In advanced cancer patients, IL-2 endogenous production has been shown to be reduced [8], so the increased TNF secretion occurring in advanced neoplasia would depend on mechanisms other than IL-2 stimulation. Recent advances in the knowledge of interactions between immune and neuroendocrine systems have demonstrated that cytokine secretion and activities depend not only on immune factors, but also on the regulatory influence exerted by several immunomodulating neurohormones [9]. In particular, the pineal hormone melatonin (MLT) [10, 11] appears to play a fundamental role in neuroimmunomodulation [12]. Moreover, preliminary data would suggest the existence of feedback mechanisms operating between the pineal release of MLT and TNF secretion [13]. Alterations of the circadian rhythm of MLT have been described in cancer patients, changes progressing with the disease [14], and this evidence could explain, at least in part, the anomalous secretion of TNF occurring in advanced neoplasia. In addition, our previous preliminary clinical studies had suggested that MLT therapy may improve the clinical conditions of untreatable metastatic cancer patients [15], by representing an effective drug in the palliative therapy of cancer. Finally, preliminary investigations would suggest that MLT may reduce TNF levels in advanced cancer patients [13].

To investigate further the relationship between MLT, TNF and neoplastic cachexia, we evaluated the influence of MLT therapy on weight loss and TNF secretion in untreatable metastatic solid tumour patients.

PATIENTS AND METHODS

The study included 100 metastatic solid tumour patients, who did not respond to previous conventional antitumour therapies, and for whom no other effective standard treatment was available. Patients with intestinal occlusion or requiring chronic infusional therapy were not included in the study. Similarly, because of the frequent occurrence of malnutrition due to the local extension of tumour, patients affected by head and neck cancers were also excluded from the study. All patients were followed at San Gerardo Hospital from January 1994 to July 1994. The experimental protocol was explained to each patient, and informed consent was obtained.

Tumour types were: lung cancer, 31; breast cancer, 19; colorectal cancer, 13; gastric cancer, 12; hepatocarcinoma, 8; pancreatic adenocarcinoma, 7; unknown primary tumour, 6; uterine cervix carcinoma, 4. Dominant metastasis sites were: soft tissues, 8; bone, 15; lung, 34; liver, 26; liver plus lung, 9; brain, 8. Patients were followed for a period of observation of 3 months, and they were considered as evaluable when observed for at least 2 months.

After stratification according to tumour type and site of disease, patients were randomised to receive supportive care alone or supportive care plus MLT. The supportive care consisted of non-steroidal anti-inflammatory agents and opioid drugs for the treatment of pain. Steroids were used only in the presence of hypotension or dyspnoea due to lung infiltration or asthmatic episodes. Dexamethasone and methylprednisolone were the corticosteroids most commonly used in supportive care. MLT was given orally at 20 mg/day in the evening, every day until the end of the study. Moreover, 13 patients (supportive care, 7; MLT group, 6) showed initial signs of respiratory distress, which was associated with pulmonary lymphangitic metastases in 10 patients. The diagnosis of respiratory distress was made on the basis of rapid and ingravescent decline in arterial p02, radiographic imaging of lung infiltrates, and no congestive heart failure as documented by echocardiogram.

To evaluate TNF secretion, venous blood samples were collected before the onset of study, and at monthly intervals for 3 months. Serum levels of TNF were measured by the RIA method using commercially available kits (Medgenix Diagnostics, Bruxelles, Belgium). The control group consisted of 40 age-matched healthy subjects. Normal values obtained in our laboratory (95% confidence limits) were 2–10 pg/ml.

Data were statistically analysed by the chi-square test, the Student's *t*-test, and the analysis of variance, as appropriate.

RESULTS

There were 86 evaluable patients, the other 14 (supportive care, 10; MLT, 4) having died from rapid disease progression. The characteristics of evaluable patients are reported in Table 1. The two groups of patients were well balanced for all main prognostic variables, including tumour types, sites of disease, age and performance status (PS), as evaluated according to Karnofsky's score.

Despite no apparent difference in food intake, a weight loss greater than 10% occurred in 13 of 41 (32%) patients treated

Table 1. Clinical characteristics of 86 evaluable untreatable metastatic solid tumour patients receiving supportive care alone or supportive care plus melatonin (MLT)

	Supportive care	Supportive care + MLT
n	41	45
M/F	27/14	29/16
Median age (years)	64 (39–74)	66 (41–76)
Median PS (Karnofsky)	60 (20–90)	60 (20–90)
Tumour types		
Non-small cell lung cancer	13	14
Breast cancer	8	6
Colorectal cancer	6	7
Gastric cancer	4	6
Hepatocarcinoma	3	4
Pancreatic cancer	3	3
Unknown primary tumour	2	3
Cervix carcinoma	2	2
Dominant metastasis sites		
Soft tissues	4	4
Bone	7	6
Lung	14	15
Liver	11	13
Lung + liver	3	4
Brain	2	3
Previous chemotherapy	39	43

by supportive care alone, and in only 2 of 45 (4%) patients concomitantly treated by MLT; this difference was statistically significant ($P < 0.01$). The mean weight loss was significantly higher in patients treated by supportive care than in patients who received MLT (16 ± 2 versus $3 \pm 1\%$, mean $\pm$ SE, $P < 0.001$). Weight loss was particularly severe in lung cancer, gastric cancer and pancreatic cancer patients, while it was less pronounced in breast cancer patients.

No MLT-related toxicity was observed. On the contrary, most patients receiving MLT experienced a relief of asthenia and/or depressant symptoms, as well as an improvement in PS. The relief of asthenia and depressant symptoms was assessed by specific patient report. For patients with clinical signs of respiratory distress death rapidly occurred in 7 of 7 patients treated by supportive care alone, and in only 1 of 6 patients who received MLT ($P < 0.05$). The other 5 patients with respiratory distress improved on MLT administration, by showing a progressive disappearance of radiological lung infiltrates and an increase in artieral pO_2.

According to WHO criteria, progressive disease (PD) was observed in 37 of 41 (90%) patients treated by supportive care alone, and in only 24 of 45 (53%) patients concomitantly treated with MLT. Therefore, the per cent of PD was significantly higher in patients treated with supportive care alone than in patients concomitantly treated with MLT ($P < 0.05$). No patient had objective tumour regression.

TNF mean serum levels observed in patients were significantly higher in cancer patients than in controls (41 ± 5 versus 6 ± 2 pg/ml, mean $\pm$ SE, $P < 0.001$). Before the onset of study, no significant difference in TNF mean levels was observed between the two groups. TNF mean serum levels progressively increased in patients receiving only supportive care but to levels that were not significantly different to pretreatment values. In contrast, mean serum concentrations of TNF decreased in patients on MLT therapy, to a value after 2 and 3 months of therapy, that was significantly lower to pretreatment levels ($P < 0.05$). Mean serum levels of TNF observed in patients treated with or without MLT in relation to changes in body weight are illustrated in Figure 1.

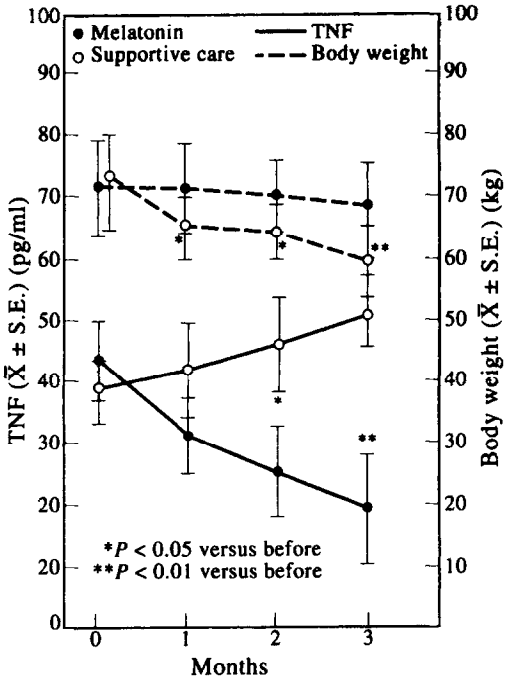

Figure 1. Changes in tumour necrosis factor-alpha (TNF) mean serum levels in relation to mean body weight in metastatic solid tumour patients treated by supportive care alone or supportive care plus melatonin.

DISCUSSION

In accordance with our previous investigations [15], this clinical study further suggests that MLT administration can improve the clinical condition of untreatable metastatic solid tumour patients, and therefore has potential value in the palliative care of human neoplasms. In addition, this study shows that MLT may counteract weight loss that occurs with progressing cancer, and that this anticachectic property of the pineal hormone is associated with a progressive decline in TNF mean concentrations. Since TNF may play a role in the pathogenesis of neoplastic cachexia, these results would suggest that MLT-induced prevention of weight loss may depend, at least in part, on its effects on TNF secretion. Previous experimental studies have suggested that MLT may inhibit the growth of some tumour cell lines [10]. On the basis of the present results, showing an inhibitory effect of MLT on TNF secretion, it is possible to suggest that MLT may influence the clinical status of advanced cancer by influencing either cancer cell proliferation, or the endogenous secretion of cytokines. Progestative agents have also been proven to be effective in the treatment of neoplastic cachexia [16], and this finding also seems to depend on an inhibitory effect on TNF secretion. However, because of the potential metabolic and cardiovascular side-effects of progestative agents, the administration of MLT, which has no documented toxicity, could be recommended as a more appropriate palliative therapy of neoplastic cachexia. Further clinical trials, comparing MLT alone or progestative alone with their combination will be required to establish which is the best medical therapy for neoplastic cachexia.

The MLT effect on disease progression could depend on its possible cytostatic action, rather than on a decline in TNF concentrations, with its potential antiproliferative action having been well documented in animals [10]. However, the influence of an imbalanced distribution of patients cannot be excluded.

Finally, even though the number of patients was low, this study seems to suggest that MLT therapy may prevent the progression of cancer-related respiratory distress. This apparent property of MLT could depend on its inhibition of TNF secretion, which has been proven to play a role in enhancing pulmonary capillary permeability responsible for the respiratory distress [17] by stimulating nitric oxide secretion [18]. Equally, MLT may directly inhibit nitric oxide production from endothelial calls, as observed in experimental conditions [19].

Obviously, a double-blind placebo study is needed to confirm the therapeutic efficacy of MLT in the treatment of neoplastic cachexia, and to establish that changes in TNF levels occurring on MLT therapy do not simply represent an epiphenomenon.

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