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A Phase-2 Study on the Kinetics of the Improvement in Lymphocyte-to-Monocyte Ratio by High-Dose Pineal Hormone Melatonin in Lymphocytopenic Untreatable Metastatic Cancer Patients

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Abstract

It is known that lymphocytopenia is one of the most negative biomarkers in cancer patients, being an expression of cancer-related immunosuppression. Today it is known that, despite its complexity, the antitumor immunity is mainly mediated by dendritic cell-T lymphocyte system and suppressed by the macrophage-regulatory T lymphocyte system. Then, lymphocyte-to-monocyte ratio (LMR) has been proven to represent a more appropriate prognostic clinical index than the simple lyphocytopenia alone. Because of the fundamental role of lymphocytes in mediating tumor cell destruction, the correction of cancer-related lymphocytopenia could influence the clinical history of the neoplastic disease. At present, the only cytokine able to induce a clear in vivo lymphocytosisis IL-2. However, it has been demonstrated that the immune system is physiologically under a neuroendocrine control, and that the pineal hormone MLT may stimulate T lymphocyte proliferation and activation. On these bases, we have evaluated the effect of high-dose MLT therapy in metastatic solid tumor patients with persistent lymphocytopenia and abnormally low values of LMR. The study included 14 patients, and the results were compared to those found in a control group of 20 lymphocytopenic untreatable metastatic cancer patients treated with the only best supportive care alone. Patients received MLT at a dose of 100 mg/day orally in the evening for 3 consecutive months. Lymphocyte mean count increases on MLT therapy, and the values observed after two months of therapy were significantly higher than the pretreatment ones, with a normalization of lymphocyte number in 4/14 (29%) patients, whereas no spontaneous lymphocyte rise occurred in the control group. On the other hand, monocyte count rapidly diminished on MLT therapy, and LMR mean values observed after only one month of treatment was significantly higher than that found prior to therapy, whereas it significantly decreases in controls. This preliminary study shows that high-dose MLT may improve the immune status of cancer patients, and be effective in the treatment of disseminated cancer-related lymphocytopenia.

Keywords: ***Antitumor immunity; Immunotherapy; Lymphocyte-to-monocyte ratio; Lymphocytopenia; Melatonin; Pinealgland***

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Introduction

Lymphocytopenia has been proven since many years to constitute one of the most negative biological prognostic factor in terms of both survival time and response to therapy [1,2]. Moreover, it has been demonstrated that cancer-related chronic inflammatory status is the main responsible for the suppression of the anticancer immune-biological response, and that it is mainly mediated by the monocyte-macrophage system, since it has been shown that tumor macrophage infiltration stimulates cancer growth through the production of tumor growth and angiogenic factors [3,4]. Monocyte count has appeared to positively correlate to tumor macrophage infiltration and to the degree of macrophage system activation [3,4], then the increase in monocyte count also constitutes a prognostically negative biomarker in cancer patients. The negative prognostic significance of both lymphocytopenia and monocytosis is not surprising, since tumor destruction is mainly a lymphocyte-dependent phenomenon [5], and cancer-related immunosuppression is namely mediated by the monocyte-macrophage system, whose degree of activation is reflected by the simple monocyte count. In more detail, cancer-related immunosuppression of the anticancer immunity is maximally realized by regulatory T lymphocytes (T reg) through the release of immunosuppressive cytokines, such as IL-10 and TGF-beta [6], which are able to inhibit the secretion of both IL-2 and IL-12, the two main antitumor cytokines in humans, but whose generation is under a macrophage stimulatory regulation [3,4,7]. Then, by considering that both lymphocytopenia and monocytosis may represent negative prognostic factors, lymphocyte-to-monocyte ratio (LMR) would have to represent a more appropriate clinical index of the immune status of cancer patients with respect to the single event of lymphocytopenia and monocytosis. In fact, the clinical studies carried out in a great number of cancer patients have confirmed that the evidence of an abnormally low LMR ratio is more precocious and appropriate negative prognostic biomarker than the simple lymphocytopenia alone [7,8]. In more detail, from a clinical point of view, three different conditions of LMR values with different prognostic significance may be identified, consisting of: 1) normal LMR values in association with normal lymphocyte count: it is the most prognostically favourable condition; 2) normal LMR values, but in association with low lymphocyte count: it is a prognostically intermediate condition; 3) abnormally LMR values, due to decline in lymphocyte count with a concomitant increase in monocyte number, which may reach values similar or superior to that of lymphocyte themselves: it is the most negative prognostic condition. Moreover, it has to be taken into consideration that at present it has been demonstrated the existence of specific growth factors for each single hematologic cell, consisting of erythropoietin for erythrocytes, GM-CSF for both monocytes and neutrophils, G-CSF for neutrophils, M-CSF for monocytes, thrombopoietin, IL-6 and IL-11 for platelets, and IL-2 for T lymphocytes, which in fact at the beginning was called as the T cell growth factor (TCGF) [9,10]. However, despite its capacity of inducing lymphocyte proliferation more than every other known cytokine [9], then its potential efficacy in the treatment of cancer by correcting lymphocytopenia because of its association with a reduced survival, IL-2 has been substantially used up to now as a simple active agent in the treatment of some tumor histotypes, namely renal cell cancer and melanoma [10], rather than as an hematopoietic growth factor to correct cancer-related lymphocytopenia and to improve the survival time by normalizing lymphocyte number, as suggested by preliminary clinical studies [11]. In addition to that of the immunotherapy with IL-2, another potential approach in the treatment of cancer-related lymphocytopenia, according to the recent advances in the Psycho-neuro-endocrino-immunology (PNEI), is represented by the possibility to influence proliferation and differentiation of lymphocytes by acting on their neuroendocrine regulation. In particular, it has been shown that lymphocyte proliferation is inhibited by corticosteroids and stimulated by the pineal indole hormone melatonin (MLT) [12,13], whose circadian secretion is maximal during the dark period of the day. Moreover, it has been demonstrated that MLT may exert a direct cytotoxic anti-proliferative effect on cancer cells, namely against MLT-receptor expressing tumors [14], and that its anticancer and immune-modulating activity is a dose-dependent

phenomenon, by reaching its potency with doses greater than 100 mg/day [15]. The clinical efficacy of MLT has appeared to be enhanced by some complementary agents, including other pineal in doles, and some anti-tumoral plants, such as Aloe, Magnolia and Myrrh. Then, it is possible to identify two possible ways to treat cancer-related lymphocytopenia, the direct immunotherapeutic way with IL-2, whose efficacy in terms of lymphocytosis may be amplified by a concomitant injection of IL-12 [16], and the neuroendocrine approach with hormones and neuro active agents capable of stimulating lymphocyte proliferation and activation, such the pineal indole MLT. On these bases, a study was planned to analyze the kinetics of changes in lymphocyte and monocyte counts under a chronic administration of high-dose MLT as a complementary medicine in metastatic cancer patients with lymphocytopenia, for whom no other standard anticancer therapy was available, because of failure of the previous treatments, including chemotherapy, endocrine therapy, biological target therapy, anti-angiogenic therapy, and immunotherapy.

Patients and Methods

The phase-2 study included 14 untreatable metastatic solid tumor patients (M/F: 8/6; median age 64 years, range 38-75). Tumor histotypes were, as follows: non-small cell lung cancer: 4; pancreatic cancer: 3; colorectal cancer; breast cancer: 2; ovarian cancer: 2. Dominant metastasis sites were, as follows: nodes: 1; bone: 1; lung: 3; liver: 4; lung plus liver: 3; brain: 2. The experimental protocol was explained to each patient, and written consent was obtained. Eligibility criteria were, as follows: histologically proven metastatic solid tumor, measurable lesions, and lack of response or progression under the common standard anticancer therapies, persistent lymphocytopenia for at least three months prior to study with lymphocyte count less than 1,000/mm^3, and LMR below the normal values of 2.1. The control group consisted of 20 untreatable metastatic solid tumor patients well comparable for age, clinical status, tumor histotypes and disease extension, who were treated with the only best supportive care alone. MLT was given orally at 100 mg once/daily during the dark period of the day, generally half-hour prior to sleep, by starting with a dose of 20 mg/day, and by reaching the planned dosage with in few days in the absence of excessive sleepiness, without interruption for three consecutive months. In the presence of an evident subjective well-being, or tumor control, MLT therapy was continued until disease progression or objective worsening of the clinical conditions. To evaluate lymphocyte and monocyte counts, and LMR, venous blood samples were collected in the morning after an overnight fast prior to study and at 15-day intervals. Normal values observed in our laboratory (95% confidence limits) were more than 1,500/mm^3 for lymphocytes, less than 500/mm^3 for monocytes, and values less than 2.1 for LMR. 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 LMR, with values greater than 2.1, was achieved in 11/14 (79%) patients under high-dose MLT therapy within 1 month of treatment, while a normalization of lymphocyte count, with values more than 1,500/mm^3, was obtained only in 4/14 (29%) patients. On the contrary, no spontaneous increase in lymphocyte count occurred in the control group. Lymphocyte and monocyte mean counts observed on MLT therapy and in controls are illustrated in (Figure 1). Monocyte mean count rapidly decrease on MLT therapy, and starting from 15 days after the onset of therapy, their mean numbers was significantly lower with respect to the values seen prior to treatment. Lymphocyte mean count also enhanced on MLT therapy, but it became significantly higher than the pretreatment values only after two months of therapy. On the contrary, lymphocyte and monocyte mean numbers decreased and increased, respectively, on time in the control group, even though without significantly differences with respect to the baseline values. However, lymphocyte and monocyte mean numbers observed in MLT group were constantly significantly higher and lower, respectively, than those seen in the control group. Changes in LMR

values observed in MLT group and in controls are illustrated in (Figure 2). LMR mean values significantly increase on MLT therapy, and their started to become statistically significantly with respect to the values prior to therapy from one month of treatment, whereas LMR mean ratio progressively decline on time, and LMR values found 60 days from the onset of the study became significantly lower than the pretreatment ones. No biological toxicity occurred on high-dose MLT.

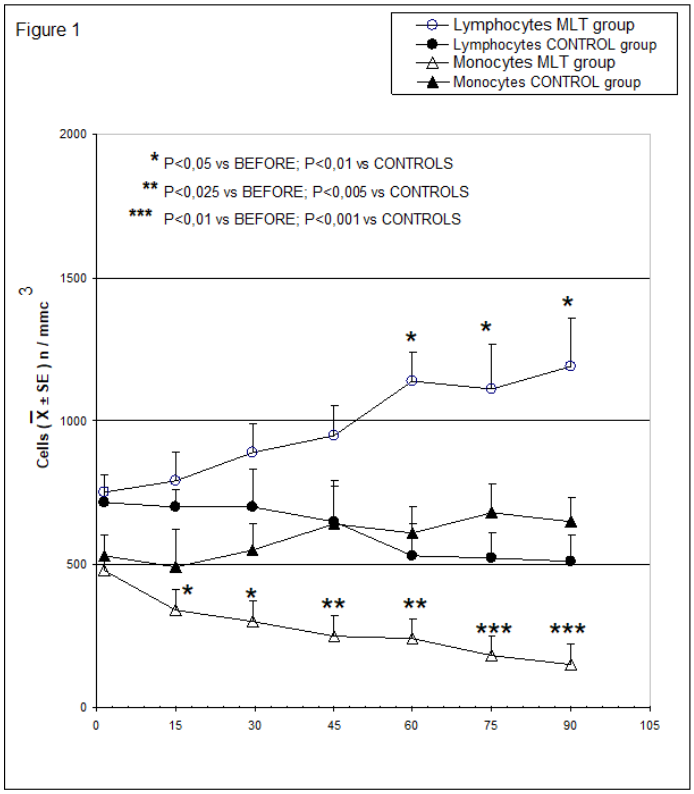

Figure 1: Lymphocyte and monocyte mean counts observed on MLT therapy and in controls.

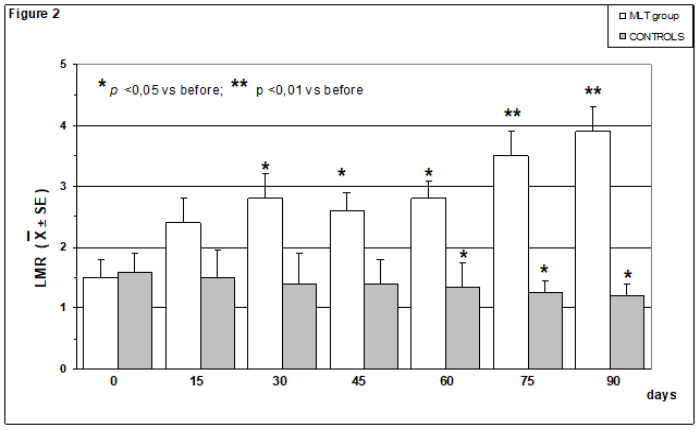

Figure 2: Changes in LMR values observed in patients treated with MLT and in controls.

Discussion

Even though with a lower efficacy and in less rapid manner with respect to the results obtained with IL-2 [17-20], this preliminary study shows that high-dose MLT may be also effective in the treatment of cancer-related lymphocytopenia in patients with disseminated cancer, and for whom no other conventional antitumor therapy was available. Obviously,

randomized studies will be required to confirm these results. However, because of no spontaneous normalization of lymphocyte count occurred in the control group, it is very probable that lymphocyte increase observed in MLT group may be due to the immune stimulating effects of MLT itself [12]. Moreover, the results of this study show that lymphocyte increase is proceeded by an evident decline in monocyte count, by suggesting that a diminished activity of the monocyte-macrophage system may constitute an essential condition for lymphocyte proliferation and activation. This statement is justified by the evidence that cancer-related immunosuppression due to T lymphocyte hypofunction is mainly depending on a macrophage system hyper activation. It is probable that more promising results in the treatment of cancer-related lymphocytopenia could be achieved by a concomitant administration of IL-2 plus MLT. However, because of its lack of toxicity and very low social cost, high-dose MLT may be used in the treatment of cancer-related lymphocytopenia, by using IL-2 in the only patients, who obtained no immune benefit on MLT therapy alone. The evaluation of the impact of lymphocytopenia correction by high-dose MLT on the survival time in untreatable metastatic cancer patients will be the aim of future successive clinical studies.

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