

## Reduction of cisplatin-induced anemia by the pineal indole 5-methoxytryptamine in metastatic lung cancer patients

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Submitted: July 29, 2002  
Accepted: August 7, 2002

Key words: **chemotherapy-induced anemia; cisplatin; methoxytryptamine; pineal indoles**

Neuroendocrinology Letters 2003; 24(1/2):83-85 pii: NEL241203A13 Copyright © Neuroendocrinology Letters www.nel.edu

### Abstract

**OBJECTIVE:** It has been demonstrated that the hematopoiesis is under a neuroendocrine control, namely mediated by the pineal gland. The pineal indole melatonin (MLT) has appeared to exert thrombopoietic and lymphopoietic activity, whereas it has no relevant effect on red cell differentiation. The present study was performed to evaluate the influence of another pineal indole, the 5-methoxytryptamine (5-MTT) on red cell line and hemoglobin production.

**MATERIALS & METHODS:** The study was carried out in metastatic lung cancer patients who underwent a chemotherapeutic combination containing cisplatin, which is known to induce anemia. The study included 20 patients treated with cisplatin plus etoposide, who were randomized to receive chemotherapy alone or chemotherapy plus 5-MTT (1 mg/day orally at noon every day).

**RESULTS:** Hemoglobin mean blood concentrations significantly decreased in both groups of patients. However, the decrease in hemoglobin levels observed in patients treated with chemotherapy alone was significantly higher with respect to that observed in patients concomitantly treated with 5-MTT. Moreover, the percent of patients who had no progressive disease on treatment was significantly higher in the group treated with chemotherapy plus 5-MTT.

**CONCLUSIONS:** Even though the low number of patients does not allow us to draw definite conclusions, these preliminary results would show that the concomitant administration of 5-MTT may reduce cisplatin-induced anemia in cancer patients, by suggesting a hematopoietic activity of 5-MTT on red cell line differentiation and hemoglobin production. Moreover, the study would suggest that 5-MTT, as well as previously demonstrated for MLT, may also enhance the cytotoxic activity of cancer chemotherapy.

## Introduction

The recent advances in the psychoneuroimmunology have demonstrated that the hematopoiesis is under a neuroendocrine control, which is mediated by several neurohormones and neuropeptides capable of influencing the proliferation and the differentiation of the various blood cell lines [1, 2]. In particular, it has been shown that the pineal gland may regulate the hematopoietic processes [1–3]. Until few years ago, most pineal investigations had been limited to the analysis of the pineal hormone melatonin (MLT), and very few biological data were available about the effects of the other less characterized pineal indoles, such as 5-methoxytryptamine (5-MTT) [4]. MLT has been proven to stimulate the production of platelets and lymphocytes [5, 6], whereas its effects on red cell line and neutrophils would be less evident. Moreover, MLT has been shown to prevent chemotherapy-induced thrombocytopenia in cancer patients [7, 8], whereas less relevant effects were seen on chemotherapy-induced neutropenia and anemia. However, it has to be remarked that MLT is not the only pineal hormone, and it would seem that the various pineal indoles may exert different effects on the different blood cell lines. In particular, preliminary clinical results would suggest that the less investigated pineal indole 5-MTT may play more pronounced effects on erythrocytes generation with respect to MLT itself [9]. Therefore, 5-MTT, in addition to a thrombopoietic activity similar to that of MLT [10], would also exert an erythropoietic function. On this basis, a clinical study was planned in an attempt to evaluate the effects of a concomitant 5-MTT administration on the anemia induced by cisplatin-containing chemotherapy in metastatic cancer patients.

## Materials and methods

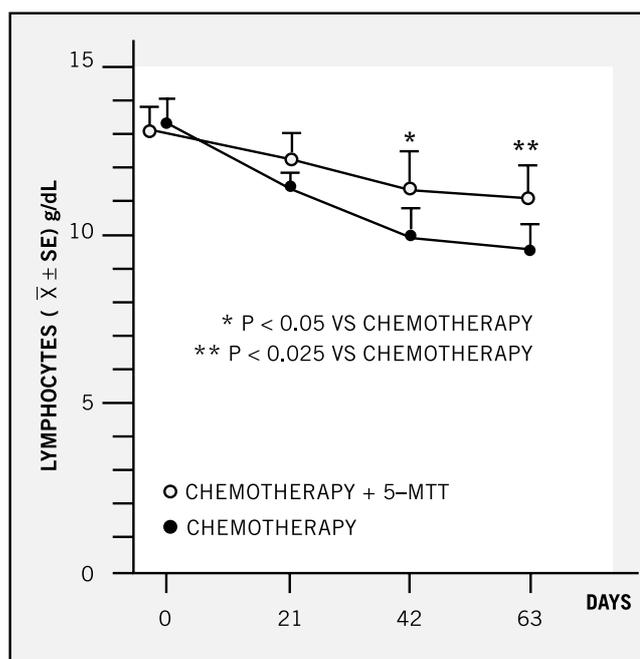
The study was performed in 20 metastatic non-small cell lung cancer (NSCLC) patients, who were randomized to be treated by chemotherapy alone or chemotherapy plus 5-MTT. The chemotherapy consisted of cisplatin (20 mg/m<sup>2</sup> I.V./day) plus etoposide (100 mg/m<sup>2</sup> I.V./day) for 3 consecutive days, corresponding to one complete chemotherapeutic cycle. Three cycles were planned at 21-day intervals. According to our previous studies [9, 10], 5-MTT was given orally at a dose of 1 mg/day at noon every day until the end of chemotherapy. Eligibility criteria were, as follows: histologically proven metastatic NSCLC, measurable lesions, no double tumor, no previous chemotherapy for the metastatic disease and no concomitant treatment with erythropoietin or other drugs potentially influencing red cell generation. The experimental study was approved by the Ethical Committee. Moreover, the protocol was explained to each patient, and written consent was obtained. The clinical response was evaluated according to WHO criteria. Finally, the results were statistically analyzed by the chi-square test, the Student's *t*-test and the analysis of variance, as appropriate.

## Results

The clinical characteristics of the two groups of patients, treated by chemotherapy alone or chemotherapy plus 5-MTT are reported in Table 1. As shown, the two groups of patients were well comparable for the overall main prognostic variables, including tumor histotype, dominant metastasis sites, age and performance status. Changes in hemoglobin mean levels observed during the chemotherapeutic treatment are illustrated in Fig.1. Before the onset of chemotherapy, no significant difference in hemoglobin mean concentrations was

**Table 1.** Clinical characteristics of metastatic non-small cell lung cancer patients treated with chemotherapy alone (cisplatin plus etoposide) or chemotherapy plus the pineal indole 5-methoxytryptamine (5-MTT).

CHARACTERISTIC	CHEMOTHERAPY	CHEMOTHERAPY + 5-MTT
n	11	9
M/F	6/5	5/4
MEDIAN AGE (years)	59 (52–68)	61 (54–71)
MEDIAN PERFORMANCE STATUS (KARNOFSKY'S SCORE)	80 (60–100)	80 (50–100)
<b>TUMOR HISTOTYPE</b>		
– EPIDERMOID CARCINOMA	4	3
– ADENOCARCINOMA	5	4
– LARGE CELL CARCINOMA	2	2
<b>DOMINANT METASTASIS SITES</b>		
– BONE	2	1
– LUNG	3	2
– LIVER	3	3
– LIVER + LUNG	2	2
– BRAIN	1	1



**Fig.1:** Changes in hemoglobin mean blood concentrations in cancer patients treated with chemotherapy alone or chemotherapy plus 5-Methoxytryptamine (5-MTT).

observed between the two groups of patients. Hemoglobin mean levels decreased during chemotherapy in both groups of patients. However, hemoglobin mean levels observed in patients treated with chemotherapy alone were significantly lower with respect to those found in patients concomitantly treated with 5-MTT ( $P < 0.025$ ). Moreover, the mean decline in hemoglobin levels was significantly higher in patients treated with chemotherapy alone than in those who received chemotherapy plus the pineal indole ( $-2.7 \pm 0.3$  vs.  $-1.6 \pm 0.2$  g/dL,  $P < 0.05$ ). As far as the clinical response is concerned, no patient achieved a complete response. A partial response (PR) occurred in 2/11 (18%) patients treated with chemotherapy alone and in 3/9 (33%) patients treated with chemotherapy plus 5-MTT. Moreover, a stable disease (SD) was obtained in 3 patients of chemotherapy group and in 5 patients treated with chemotherapy plus the pineal hormone, whereas the remaining 6 patients treated with chemotherapy alone and one patient treated with chemotherapy plus 5-MTT had a progressive disease (PD). Therefore, the percent of non-PD (PR + SD) achieved in patients concomitantly treated with the pineal indole was significantly higher with respect to that observed in patients who received chemotherapy alone (8/9 vs. 5/11,  $P < 0.05$ ). Finally, chemotherapy was subjectively well tolerated in patients concomitantly treated with 5-MTT. In particular, the percent of asthenia and/or anorexia which occurred in patients treated with chemotherapy alone was significantly higher than that observed in patients concomitantly treated with the pineal indole (8/11 vs. 3/9,  $P < 0.05$ ).

### Discussion

Even though the low number of patients does not allow us to draw definite conclusions, this preliminary clinical study would suggest that the concomitant administration of the less investigated pineal neurohormone 5-MTT may reduce cisplatin-induced anemia in metastatic cancer patients, by further remarking the hematopoietic properties of the pineal gland and of its indole hormones. Therefore, whereas the most investigated pineal indole MLT would play hematopoietic activity particularly on platelet generation, the other pineal indole 5-MTT would seem to be active also on red cell line proliferation. The mechanisms responsible for the apparent erythropoietic activity of 5-MTT need to be investigated and defined, and in particular it will have to be established whether they may consist at least in part of a stimulation of erythropoietin secretion, which is the main growth factor for red cell line proliferation and differentiation [11]. In any case, the results of this study would further confirm the fundamental role of the pineal gland in the central psycho-neuroendocrine regulation of the hematopoietic processes, as previously demonstrated with MLT for the thrombopoietic differentiation [5–8]. In addition, even though these results will have to be confirmed in a greater number of cancer patients, this study seems to suggest that the concomitant administration of 5-MTT may enhance the antitumour efficacy of chemotherapy

in metastatic solid neoplasms, as previously demonstrated with MLT [7, 8]. This finding is not surprising and it may be explained on the basis of the antioxidant activity of both: MLT and 5-MTT [12]. In fact, the antioxidant agents have appeared to increase the cytotoxic anticancer action of the chemotherapeutic drugs [13]. Moreover, the immunomodulating properties played by both MLT and 5-MTT [14] may also contribute to enhance the antitumour efficacy of cancer chemotherapy. Then, the clinical use of 5-MTT in the medical Oncology may allow us to elaborate chemoneuroendocrine regimens in the treatment of human neoplasms, by further extending the already interesting results obtained with chemotherapy plus the better investigated pineal indole MLT [7,8].

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