

# A study of a possible cancer cure by correcting the main cancer-related psychoneuroendocrine alterations responsible for tumor-related immunosuppression

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## Abstract

It is known since more than 50 years that the pineal gland plays a fundamental anticancer physiological role by releasing hormones capable of counteract cancer growth by either inhibiting cancer cell proliferation, or stimulating the antitumor immunity, as well as that cancer progression is constantly associated with a progressive decline in the pineal endocrine function. Despite the well demonstrated antitumor activity of the pineal gland and the complete absence of biological toxicity and the low cost of the antitumor pineal molecules, surprisingly very few clinical studies have been carried out up to now with pineal hormones in the treatment of human neoplasms, at least in patients, for whom no other conventional anticancer therapy may be available. The present study was carried out to evaluate the therapeutic effects of a pineal endocrine substitution therapy with high-dose melatonin (MLT) alone (n=68), MLT plus 5-methoxytryptamine (5-MTT) (n=72) or MLT plus 5-MTT plus pinealine (PNL) (n=28) in 168 untreatable metastatic solid tumor patients with life expectancy less than 1 year. A survival longer than 1 year was achieved in 72/168 (43%), and both objective tumor regression rate and 1-year survival observed in patients treated with MLT plus other pineal hormones were higher than in patients treated by MLT alone, without, however, statistically significant differences. On the contrary, the percentage of disease control (DC) obtained by MLT plus other pineal molecules was significantly higher than that achieved by MLT alone. The clinical status improved in most patients. Finally, lymphocyte count and lymphocyte-to-monocyte ratio enhanced in patients with DC, whereas a further decline occurred in patients with PD. This preliminary study shows that a pineal endocrine therapy may improve the prognosis of metastatic cancer patients, including those for whom no other standard anticancer therapy is available, and that the control of the neoplastic disease may be further enhanced by associating to MLT other less investigated antitumor pineal hormones.

## Introduction

After a long time of conflicting results, today there is no doubt about the possibility to treat the human neoplasms by acting on the immune system [1]. The control of cancer growth by stimulating host anticancer immunity is now a real clinical approach on the basis of three main evidence, consisting of the immunosuppressive effect of macrophage-mediated chronic inflammatory response [2], the generation of regulatory T lymphocytes (T<sub>reg</sub>) able to suppress the anticancer immunity [3], and the existence of immune inhibitory checkpoints, mainly consisting of CTLA-4 [4], PD-1 and its ligands PD-L1 and PD-L2 [5], which are expressed by T lymphocytes and tumor cells themselves, and whose activation may suppress both antigen-specific and non-specific anticancer immunity [6]. The *in vivo* activation of an effective anticancer immunity may be obtained through the administration of antitumor cytokines, such as IL-2 [7] and IL-12 [8], or that of anti-inhibitory checkpoint monoclonal antibodies [4,5]. However, more recent investigations have shown that the *in vivo* immune responses, including the anticancer immunity, is physiologically under a psychoneuroendocrine control [9,10], which is the neurochemical expression of the psychospiritual life [11]. In more detail, the anticancer immunity has appeared to be inhibited by the brain opioid system, mainly through mu-opioid receptor [12], and to be stimulated by the pineal gland through its main indole hormone melatonin (MLT) [13]

and other less investigated indole and beta-carboline molecules [14,15]. Moreover, it is known since many years that cancer progression is constantly associated with a progressive decline in the pineal endocrine function in both animals and humans [16], with a following progressive decline in the nocturnal production of MLT. Because of the stimulatory effect of MLT on the anticancer immunity, with stimulatory effects of T-helper lymphocytes (TH) and inhibitory ones on macrophage-mediated immunosuppression [13], the main cancer-related immune alterations, including low levels of IL-2 and high concentrations of IL-6 [17], could depend at least in part on the progressive cancer-related pineal hypofunction and low MLT blood levels. In fact, preliminary clinical studies have shown that the chronic administration of mild pharmacological doses of MLT, consisting of about 20 mg, once / daily during the dark period, may improve the immune status and prolong the survival time in metastatic cancer patients with life expectancy less than 6 months, and for whom no other standard anticancer treatment

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was available [18,19]. Moreover, the association of MLT has been proven to enhance the antitumor efficacy of IL-2 cancer immunotherapy [20]. However, it has to be remarked that MLT is not the only hormone produced by the pineal gland, since at least two other pineal molecules have appeared to play anticancer activity, the 5-methoxytryptamine (5-MTT) and the beta-carboline 6-methoxy-1,2,3,4-tetrahydro-beta carboline, also called pinealine (PNL) [14,15]. Histological damages of the pineal gland have been observed in patients died from cancer [21]. Then, it is probable that cancer progression-related pineal deficiency does not involve the only MLT secretion, but that of the overall pineal hormones. Therefore, an eventual pineal substitutive endocrine therapy would include at least the administration of MLT, 5-MTT and PNL. In addition, the anticancer effects of MLT has been recently proven to be a dose-dependent phenomenon in humans [19]. On this basis, a clinical study was planned to evaluate the therapeutic anticancer effects of MLT alone, MLT plus 5-MTT, and MLT plus 5-MTT and PNL in metastatic cancer patients, for whom no other conventional anticancer therapy was available.

## Materials and methods

The study was performed to compare the results achieved during different clinical investigations in three different groups of untreatable metastatic solid tumor cancer patients, who had received high-dose MLT alone (group A; n=68), high-dose MLT plus 5-MTT (group B; n=72), and high-dose MLT plus 5-MTT plus PNL (group C; n=28), for a total of 168 patients. MLT was given at very-pharmacologically doses because of its demonstrated dose-dependent anticancer potency in humans [19]. On the contrary, 5-MTT and PNL were given at doses corresponding about to their whole daily production with substitute intention in an attempt to correct a probable their deficiency with cancer progression, as shown in experimental conditions [16,21]. The experimental protocol was explained to the patients and their consent was obtained. Eligibility criteria were, as follows: histologically proven metastatic solid tumor, measurable lesions, no availability of other standard anticancer therapy, including chemotherapy, endocrine therapy, anti-angiogenic treatments, target therapy and immunotherapy, because of lack of response to previous treatments or poor clinical conditions unable to sustain specific anticancer therapies, no abdominal occlusion and life expectancy less than 1 year or less than 6 months in some cases. All treatments were given orally and once/daily in relation to the different phases of the photoperiod. MLT was given at 100 mg/day in the dark, about 30 minutes before sleeping, 5-MTT was given at 5 mg/day in the period of light at about 1 P.M., and finally PNL was given at 1 mg/day at about 8 P.M. or about 3 hours before sleeping. The treatment was continued without interruption until disease progression, by repeating the main radiological examinations every 3 months for the first year, including CT scan, NMR and PET, then every 6 months. In addition as palliative therapy because of their potential anti-inflammatory and analgesic effects [22-24], the supportive treatment consisted of Aloe arborescens/Myrrh mixture (60:40) at 10 ml twice/day and Magnolia cortex with honokiol concentration more than 50% at 500 mg twice/day. The clinical results were evaluated according to WHO criteria at 3-month intervals. Moreover, because of its recently demonstrated capacity of reflecting the anticancer immune status of patients, from a laboratoristic point of view, patients were monitored by evaluating lymphocyte-to-monocyte ratio (LMR) as useful inexpensive biomarker provided by prognostic significance [25]. Normal values obtained in our laboratory (95% confidence limits) were more than 1,500/mm<sup>3</sup> for lymphocytes and values greater than 2.1 for the LMR. Data were reported as mean  $\pm$  SE, and statistically analyzed by the chi-square test and the Student's t test, as appropriate.

## Results

The clinical characteristics of the three groups of patients are reported in Table 1. As shown, the three groups of patients were well balanced for the main prognostic clinical variables, including age, disease extension, tumor histotype, metastatic sites and clinical status. The clinical results achieved in the different groups of patients are reported in Table 2. According to WHO criteria, a complete response (CR) was obtained in 4/168 (2%) patients (group A: 1 (biliary tract cancer); group B: 2 (lung adenocarcinoma: 2); group C: 1 (gastric cancer)). A partial response occurred in other 12/168 (7%) patients (group A: 3 (biliary tract cancer: 1; colon cancer: 1; pancreatic cancer: 1); group B: 6 (colorectal carcinoma: 2; epidermoid lung cancer: 1; pancreatic cancer: 1; bladder cancer: 1; biliary tract cancer: 1); group C: 3 (melanoma: 1; triple negative breast cancer: 1; colorectal cancer: 1). Therefore, an objective tumor regression (CR + PR) was obtained in 16/168 (9%) patients. Moreover, tumor regression rate obtained in the groups B and C, treated respectively by MLT plus 5-MTT and MLT plus 5-MTT plus PNL, was higher with respect to that found in the group A treated with the only MLT, without, however, statistically significant differences (group A: 4/68 (6%); group B: 8/72 (11%); group C: 4/28 (14%)). A stable disease (SD) occurred in 90/168 (54%) patients (group A: 31/68 (46%); group B: 41/72 (57%); group C: 18/28 (64%)). The disease control (DC), including CR, PR and SD, was obtained in 106/168 (63%), whereas the remaining 62/168 (37%) patients had a progressive disease (PD). Moreover, the percentage of DC achieved in patients concomitantly treated by MLT plus 5-MTT was statistically significantly higher than that found in patients, who received MLT alone (49/72 (68%) vs 35/68 (51%),  $P$  0.05). The higher percentage of DC was observed in the group C treated by MLT plus 5-MTT plus PNL (JHK22/29 (78%)), even though the difference was not statistically significant with respect to the results found in the group B of MLT plus 5-MTT because of the low number of group C patients. Finally, as far as the survival time, after a follow up of at least 1 year, a survival longer than 1 year was obtained in 72/168 (43%). The percentage of 1-year survival was greater in groups B and C than in the group A, even though the difference did not reach the statistical significance. Almost all patients of the three groups referred an improvement in mood, sleep disorders, asthenia, and anorexia. The most evident improvement was seen in the group of patients also treated by PNL, particularly in the self-consciousness state. A low symptomatology of extra-sensorial perceptions was referred by 2/28 (8%) patients treated with PNL, without, however, any concomitant anxiety. Finally, as far as the immunobiological profile is concerned, as shown in Table 3, irrespectively of the type of therapy, both lymphocyte count and LMR pretreatment mean values were lower in patients who had a PD than in those with DC, without, however, statistically significant differences. On the contrary, both lymphocyte mean number and LMR mean values observed after three months of therapy at the same time of the first radiological evaluation were significantly higher in patients who achieved a DC than in those, who had a PD within the same group of therapy.

## Discussion

This preliminary clinical study, carried out in metastatic cancer patients with life expectancy less than 1 year because of no availability of other standard antitumor therapies, would show a progressive increase in the antitumor efficacy of a pineal endocrine cancer therapy by a progressive substitution treatment with pineal indole other than MLT, such as 5-MTT, and pineal antitumor beta-carbolines, such as PNL, in an attempt to counteract a probable cancer progression-

**Table 1.** Clinical characteristics of metastatic cancer patients treated with melatonin (MLT) alone (group A), MLT plus 5-methoxytryptamine (5-MTT) (group B), and MLT plus 5-MTT plus pinealine (PNL) (group C)

Characteristics	n (n=168)	MLT (n=68)	MLT + 5-MTT (n=72)	MLT + 5-MTT + PNL (n=28)
Median age (years)		68 (42-85)	65 (34-92)	67 (44-86)
Sex (M/F)		38/30	37/35	13/15
Median PS (Ecog)		1 (0-3)	1 (0-3)	1 (0-3)
<b>Tumor histotype</b>				
- Lung cancer	35	16	15	4
- Colorectal cancer	25	9	12	4
- Pancreas cancer	26	10	11	5
- Gastric cancer	10	4	5	1
- Biliary tract cancer	20	11	7	2
- Urinary tract tumors	9	4	3	2
- Gynecologic tumors	15	6	6	3
- Breast cancer	10	2	4	4
- Triple negative	6	0	2	4
- No triple negative	4	2	2	0
- Soft tissue sarcoma	10	4	5	1
- Melanoma	8	2	4	2
<b>Distant organ metastas</b>				
-Soft tissues	15	5	8	2
-Bone	11	6	4	1
-Lung	36	13	15	8
-Liver	43	18	17	8
-Liver plus lung	21	9	8	4
-Peritoneum	18	8	8	2
-Brain	24	9	12	3

**Table 2.** Clinical response (WHO criteria), and 1-year survival in untreatable metastatic solid tumor patients treated by melatonin (MLT) alone (group A), MLT plus 5-methoxytryptamine (5-MTT) (group B) or MLT plus 5-MTT plus pinealine (PNL)

Patients	Clinical response*							1-year survival
	n	CR	PR	CR + PR	SD	DC	PD	
Group A (MLT)	68	1	3	4 (6%)	31	35 (51%)	33	26 (38%)
Group B (MLT + 5MTT)	72	2	6	8 (11%)	41	49 (68%)*	23	31 43%)
Group C (MLT+5-MTT+PNL)	28	1	3	4 (14%)	18	22 (78%)*	6	15 (53%)

\*CR: Complete response; PR: Partial response; SD: Stable disease; DC: Disease control; PD: Progressive disease.

\*\* P<0.05 vs group A; P<0.01 vs group A.

**Table 3.** Lymphocyte mean number and lymphocyte-to-monocyte ratio (LMR) before therapy and after 3 months of treatment in metastatic solid tumor patients treated with MLT, MLT + 5-MTT or MLT + 5-MTT plus PNL in relation to the clinical response, consisting of progressive disease (PD) or disease control (DC)

Patients	n	Lymphocytes n/mm3 (X±SE)		LMR (X±SE)	
		Before	After	Before	After
MLT	68	1,346±188	1,541 ± 165	2.3±0.3	2.5±0.4
-DC	35	1,585±216	1,788±141	2.7±0.4	3.3±0.3*
-PD	33	1,208±209	1,176±215	2.1±0.5	1.8±0.4
MLT+5-MTT	72	1,442±176	1,544±161	2.4±0.4	2.8±0.3
-DC	49	1,639±164	1,848±144	2.8±0.5	3.6±0.3**
-PD	33	1,136±228	988±94	2.2±0.4	1.9±0.4
MLT+5-MTT+PNL	28	1,284±218	1,467±188	2.1±0.5	2.7±0.4
-DC	22	1,637±158	1,843±145	2.3±0.5	3.5+/- 0.3**
-PD	6	1,093±287	941±134	1.9±0.4	1.6±0.5

\* P<0.05 vs patients with PD; \*\* P<0.01 vs patients with PD.

related pineal deficiency, which could involve the whole endocrine activity of pineal itself [21]. This finding is not surprising, since cancer progression would not be characterized by a decline in MLT nocturnal

production, but also by a progressive pineal histological damage, with a following probable deficiency of antitumor pineal hormones other than MLT, namely 5-MTT and PNL. In fact, in tumor-bearing pinealectomized animals, the exogenous administration of MLT has appeared to abolish some but not the overall pro-tumoral effects induced by the pinealectomy, by confirming the existence of pineal antitumor hormones other than MLT itself [26]. If successive randomized studies will confirm the greater anticancer efficacy of the administration of more pineal antitumor hormones with respect to the only MLT, the total pineal endocrine replacement therapy could constitute a new simple inexpensive non-toxic cancer cure to achieve a control of the neoplastic growth by reestablishing the physiological neuroendocrine mechanisms responsible for the neuroendocrine control of cancer onset and growth in the health conditions, mainly played by the pineal, though either an inhibitory effects on cancer cells proliferation, or by piloting the immune responses in an antitumor way. In fact, in addition to the well demonstrated inhibitory effects of several pineal hormones on cancer cell proliferation and dissemination, this preliminary study would suggest that the pineal hormones may act in an antitumor way by also improving the immune status of patients, because of the evidence that the control of disease was constantly associated with an improvement in the antitumor immunity, as shown by the increase in patients, who achieved disease stabilization or tumor regression in both lymphocyte count and LMR values, which are two common prognostic biomarkers to evaluate the immune status of cancer patients and to predict their prognosis [25].

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