

Total pineal endocrine substitution therapy (TPEST) as a new neuroendocrine palliative treatment of untreatable metastatic solid tumor patients: A phase II study

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Abstract

OBJECTIVES: It is known since many years that the pineal gland plays an anti-cancer role, and melatonin (MLT), the most investigated pineal hormone, has been proven to exert antitumor activity. However, MLT would not be the only hormone responsible for the antitumor action of the pineal gland. In fact, recent advances in the pineal investigations have shown that pineal indoles other than MLT may also exert anticancer activity, namely the three main indoles, consisting of 5-methoxytryptamine (5-MTT), 5-methoxytryptophol (5-MTP) and 5-methoxy-indole acetic acid (5-MIA). Cancer progression has appeared to be associated with a concomitant decline in the pineal endocrine function. Therefore, the replacement of a complete pineal function in the advanced cancer patients would require the exogenous administration of the overall four pineal indoles. Several clinical studies have shown that MLT alone at pharmacological doses may induce a control of the neoplastic progression in about 30% of untreatable metastatic solid tumor patients. The present study was performed in an attempt to evaluate the therapeutic of a total pineal endocrine substitution therapy with its four indole hormones in cancer patients, for whom no other conventional therapy was available. **METHODS:** The study included 14 metastatic solid tumor patients, who had failed to respond to the conventional anticancer therapies. The pineal indoles were given orally according to a schedule elaborated in an attempt to reproduce their physiological circadian secretion during the daily photoperiod. MLT was given at 20 mg/day during the night, whereas the other indoles were given at 1 mg/day, by administering 5-MIA in the morning, 5-MTP at noon and 5-MTT in the afternoon. **RESULTS:** A disease-control was achieved in 9/14 (64%) patients, consisting of partial response (PR) in one patient and stable disease (SD) in the other 8 patients. The median time of disease-control (PR + SD) was 6 months (range: 4-10). **CONCLUSIONS:** This preliminary study shows that a total pineal endocrine replacement therapy by an exogenous administration of the overall four pineal indoles may induce a disease-control in about 60% of untreatable metastatic solid tumor patients. Then, these results would be clearly superior with respect to those described with MLT alone, by confirming in humans that MLT is not the only hormone responsible for the anticancer property of the pineal gland. Since Cartesius was the first author who suggested the fundamental role of the pineal in the connection between consciousness and biological life, this therapy could be defined as a Cartesian therapy.

Introduction

Several clinical and experimental studies have demonstrated that cancer development is constantly associated with a progressive decline in the pineal endocrine function [1–4]. Therefore, the pineal hypofunction would constitute the main cancer-related endocrine deficiency. Because of the well documented anticancer role of the pineal gland [5–8], cancer-related hypopinealism would not simply represent an epiphenomenon of the neoplastic disease, but it could be responsible at least in part for cancer cell proliferation and dissemination.

The pineal gland has been proven to release several endocrine substances, but the most typical pineal hormones are represented by the four major indole hormones, consisting of melatonin (MLT), 5-methoxytryptamine (5-MTT), 5-methoxytryptophol (5-MTP), and 5-methoxy-indole acetic acid (5-MIA). Even though controversial data exist [9,10], the four pineal indoles show a circadian secretion, and they would be released in different amounts in relation to the main phases of the photoperiod.

MLT is mainly released during the night [1–12], 5-MTP during the period of maximum light, 5-MTT in the afternoon before the onset of darkness, and 5-MIA in the morning at the beginning of the light period, by reproducing the four major phases of the daily photoperiod. At present, a diminished production particularly during the night in relation to cancer progression has been well demonstrated for the only MLT [1–8], and the metastatic disease is generally characterized by a complete abrogation of the physiological circadian secretion of MLT, with highest levels during the dark phase and lowest concentrations during the period of maximum light. However, because of the same enzymatic pathways and the evidence of histological features of the

pineal gland suggesting a functional damage in patients died from cancer [13]. *In vitro*, the all four pineal indoles have appeared to exert an antiproliferative oncostatic action on several cancer cell lines [14], and the most active of them in terms of antitumor activity seems to be the 5-MTT, followed by MLT, by 5-MTP and finally by 5-MIA, which would be the less active anticancer pineal indole. In addition, the antiproliferative activity would not represent the only mechanism responsible for the anticancer effects of the pineal indoles. In fact, at least for MLT and 5-MTT a clear immunostimulating property has been demonstrated [15–17]. MLT would mainly act by activating T helper-1 lymphocytes [15, 16], with a following enhanced release of the anticancer cytokine interleukin-2 (IL-2), whereas the immunomodulating activity of 5-MTT would mainly depend on a regulatory effect on the macrophage functions, with amplification of their potential anticancer action and inhibition of the great variety of their immunosuppressive activity [17], namely consisting of the release of immunosuppressant substances, such as interleukin-6 (IL-6). Preliminary results would also suggest an immunomodulatory effect of 5-MTP [18], whereas no data are available about the possible immunoregulatory role of 5-MIA. MLT has been widely used as a natural anticancer molecule in the palliative therapy of advanced cancer patients, for whom no other standard antitumor therapy is available, and no toxicity has been reported even at highly pharmacological doses [17]. According to our previous clinical results [19], MLT alone has appeared to be able to induce a control of the neoplastic progression in about 30% of metastatic cancer patients, who did not respond to previous conventional anticancer treatments and for whom no other standard therapy was available.

At present, however, there are no data about the impact on cancer progression, which may be achieved

Table 1. Clinical characteristics and individual clinical response (WHO criteria) of 14 metastatic tumor patients to a total pineal endocrine replacement therapy.

Cases	Sex	Age	Tumor Histotype	Sites Of Metastases	Ps	Previous ** Therapies	Clinical Time To Progression	Response (Months) ***
1	M	74	Colon cancer	Liver, lung	70	FUFA, FOLFOX, CPT-11	SD	10+
2	M	78	Gastric cancer	Peritoneum	60	FUFA	PD	—
3	F	58	Renal cancer	Lung, bone, nodes	100	IL-2, IFN	SD	9+
4	F	62	Non-small-cell lung cancer	Lung, bone, nodes	80	PE, VNB, GEM, MLT	SD	6
5	M	64	Renal cancer	Brain, lung, bone	70	IL-2, IFN, MLT	SD	5
6	M	61	Pancreatic cancer	Liver	100	FUFA, GEM, MLT	SD	6+
7	M	74	Unknown primary tumor	Peritoneum	80	FUFA, MLT	PR	4
8	M	64	Thymic carcinoma	Liver, lung, nodes	90	PAC, MLT	PD	—
9	M	83	Colon cancer	Liver	80	FUFA, CPT-11, MLT	PD	—
10	F	61	Breast cancer	Lung, bone	80	CMF, ADM, TXT, TAM, MLT	SD	6+
11	M	66	Prostate cancer	Bone, nodes	70	LHRH, BCL	SD	4
12	M	71	Colon cancer	Liver, peritoneum	90	FUFA, CPT-11, MLT	PD	—
13	F	59	Breast cancer	Bone marrow, peritoneum	70	CMF, ADM, TXT, MLT	PD	—
14	M	62	Non-small-cell lung cancer	Lung, nodes	70	VNB, GEM	SD	5+

* PS: Performance status (Karnofsky's score)

** FUFA: 5-Fluorouracil, Folate; CPT-11: Irinotecan; FOLFOX: 5-Fluorouracil, Folate, Oxaliplatin; IL-2: Interleukin-2; IFN: Interferon; PE: Cisplatin, Etoposide; VNB: Vinorelbine; GEM: Gemcitabine; MLT: Melatonin; PAC: Cisplatin, Adriamycin; Cyclophosphamide; CMF: Cyclophosphamide, Methotrexate, 5-Fluorouracil; ADM: Adriamycin; TXT: Taxotere; TAM: Tamoxifen; LHRH: Triptorelin; BCL: Bicalutamide

*** PR: partial response; SD: stable disease; PD: progressive disease.

through a complete pineal endocrine substitution by administering the overall four pineal indoles, and in particular it is still unknown whether a greater therapeutic efficacy may be achieved with the four pineal indoles with respect to the results obtained with MLT alone. The present study was carried out to evaluate the efficacy and tolerability of a total pineal endocrine substitution therapy (TPEST) through an exogenous administration of the overall four pineal indoles in untreatable metastatic solid tumor patients, for whom no other effective therapy was available, because of their progression on standard anticancer chemotherapy, endocrine therapy and immunotherapy.

Materials and methods

This phase II study included 14 consecutive untreatable metastatic solid tumor patients (M/F: 10/4; median age: 64 years, range 58–83), who did not respond to previous conventional treatments. Eligibility criteria were, as follows: histologically proven metastatic solid tumor, measurable lesions, no double tumor, lack of response to previous standard therapies, life expectancy less than 6 months, and no concomitant therapy with other potential immunomodulating substances. The experimental protocol was explained to each patient, and written consent was obtained. Tumor histotypes were, as follows: colorectal cancer: 3; non-small-cell lung cancer: 3; renal cell cancer: 2; breast cancer: 2; gastric cancer: 1; pancreatic cancer: 1; thymic carcinoma: 1; prostate cancer: 1; unknown primary tumor: 1. Dominant metastasis sites were, as follows: bone: 1; lung: 4; liver: 2; lung plus liver: 2; brain plus lung: 1; liver plus peritoneum: 1; bone marrow plus peritoneum: 1; peritoneum: 2. According to Karnofsky's score, the median performance status (PS) was 80% (range: 60–100). Finally, 9/14 (64%) patients had been previously already treated with MLT alone. The overall pineal indoles were supplied by Sigma-Aldrich Chemie GmbH (Schnelldorf, Germany). The pineal indoles were given orally every day until disease progression. Moreover, in an attempt to reproduce their circadian secretion, 5-MIA was administered during the morning, 5-MTP at noon, 5-MTT during the early afternoon and MLT during the dark period of the day. The daily doses were 20 mg for MLT, and 1 mg for each other pineal indoles. The dose of 1 mg for each indole other than MLT is not pharmacological, but it is that corresponding to the whole 24-hour production by the pineal gland. So, this schedule has utilized 5-MTT, 5-MTP and 5-MIA as a replacement pineal endocrine therapy and the only MLT at pharmacological doses. The use of the other pineal indoles at low substitutive doses rather than at higher pharmacological amounts is justified by their possible psychotropic effects, which are still unknown in humans. The clinical response was evaluated according to WHO criteria, and the patients were considered as evaluable when they were treated for at least two consecutive months. Data were statistically analyzed by the chi-square test.

Table 2. Clinical response (WHO) achieved in 14 untreatable metastatic solid tumor patients to a total pineal endocrine replacement therapy.

Clinical Response *		
CR	0/14	
PR	1/14	(7%)
SD	8/14	(57%)
DISEASE CONTROL (PR + SD)	9/14	(64%)
PD	5/14	(36%)
MEDIAN TIME TO PROGRESSION (months)	6	(4–10+)

* CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Results

All patients were available for the clinical response. The clinical characteristics of patients and their individual clinical response are reported in Table 1, while the overall clinical response is shown in Table 2. No complete response was observed. A partial response (PR) was achieved in one patients with peritoneal metastases due to unknown primary tumor. Moreover, a stable disease (SD) was obtained in 8/14 (57%) patients (non-small-cell lung cancer: 2; renal cell cancer: 2; breast cancer: 1; prostate cancer: 1; colon cancer: 1; pancreatic cancer: 1). Then, a disease-control (PR+SD) was achieved in 9/14 (64%) patients, whereas the remaining 5/14 (36%) patients had a progressive disease (PD). The median duration of disease-control was 6 months (range: 4–10+). The percent of disease-control was higher in patients who had not been previously treated with MLT alone than in those pre-treated with the MLT only, without, however, statistically significant differences (4/5 vs. 5/9). Moreover, within the group of patients previously treated with MLT alone, a more evident improvement in their coenesthesia was observed in 4/9 (44%) patients during the treatment with the overall pineal indoles with respect to that previously referred on MLT alone. Finally, an improvement in PS greater than 10% was achieved in 8/14 (57%) patients, and it was significantly higher in patients with disease-control than in those with PD (7/9 vs. 1/5, $P < 0.05$).

Discussion

By now, MLT is a reality in the clinical Oncology from either a physiopathological or a therapeutic point of view [5, 19–21]. In addition to the anticancer properties of MLT, this preliminary study would suggest that pineal indoles other than MLT may also exert a control on the neoplastic progression, and the therapeutic results which may be achieved with the administration of the overall main four pineal indoles in terms of both disease control and quality of life would seem to be superior to those described with MLT alone in the same kind of patients [19, 21]. In fact, the percent of control

of the neoplastic progression, which may be achieved with MLT alone in untreatable metastatic solid tumor patients, is generally less than 30%, whereas this study of TPEST shows a percent greater than 60% of disease-control. Therefore, this preliminary clinical study would agree with previous experimental results, showing that the stimulation of cancer growth induced by the surgical pinealectomy may be only partially abrogated by the exogenous administration of MLT alone [22]. Therefore, this finding would suggest the existence of anticancer pineal substances other than MLT itself, such as the other three pineal indoles. Then, whereas until few years ago the anticancer role of the pineal gland was believed to depend only on MLT, which was considered as the only active pineal hormone, at present it is known that the pineal gland may release at least three other active indoles, whose biological properties would contribute to the anticancer function of the pineal gland, as suggested by this preliminary study. Therefore, the TPEST could constitute a new effective bio-neuroendocrine approach at least as a palliative therapy of cancer in patients whom no other conventional treatment may be available. Four hundred years after Cartesius, who was the first author to hypothesize the pineal gland as the link between the spiritual consciousness and the biological life, this study would represent the first historical approach to realize a complete pineal endocrine substitution by an exogenous administration of the overall pineal indoles, by confirming the effective role of the pineal gland in the psychoneuroendocrine modulation of the biological systems. Therefore, in memory of Cartesius, we could define this complete replacement therapy of the pineal indoles as a Cartesian therapy.

- 11 Vigano D, Lissoni P, Rovelli F, et al. A study of light/dark rhythm of melatonin in relation to cortisol and prolactin secretion in schizophrenia. *Neuroendocrinol Lett.* 2001; **22**:137-41.
- 12 Iguchi H, Kato KI, Ibayashi H. Age-dependent reduction in serum melatonin concentrations in healthy human subjects. *J Clin Endocrinol Metab* 1982; **55**:27-29.
- 13 Hadjiu SI, Porro RS, Lieberin PH, Foote FW. Degeneration of the pineal gland of patients with cancer. *Cancer* 1972; **29**:706-709.
- 14 Sze SF, Ng TB, Liu WK. Antiproliferative effect of pineal indoles on cultured tumor cell lines. *J Pineal Res* 1993; **14**:27-33.
- 15 Conti A, Maestroni JGM. The clinical neuroimmunotherapeutic role of melatonin in oncology. *J Pineal Res* 1995; **19**:103-110.
- 16 Guerrero JM, Reiter RJ. Melatonin-immune system relationships. *Curr Topics Med Chem* 2002; **2**:167-180.
- 17 Sze SF, Liu WK, Ng TB. Stimulation of murine splenocytes by melatonin and methoxytryptamine. *J Neural Transm Con Sect* 1993; **94**:115-126.
- 18 Lissoni P, Fumagalli L, Paolorossi F, et al. Anticancer neuroimmunomodulation by pineal hormones other than melatonin: preliminary phase II study of the pineal indole 5-methoxytryptophol in association with low-dose IL-2 and melatonin. *J Biol Regul Homeost Agents* 1997; **11**:119-122.
- 19 Lissoni P. Is there a role for melatonin in supportive care? *Supp Care Cancer* 2002; **10**:110-116.
- 20 Lissoni P, Rovelli F, Frassinetti A, et al. Oncostatic activity of pineal neuroendocrine treatment with the pineal indoles melatonin and 5-methoxytryptamine in untreatable metastatic cancer patients progressing on melatonin alone. *Neuroendocrinol Lett.* 2000; **21**:319-323.
- 21 Lissoni P, Rovelli F, Malugani F, et al. Anti-angiogenic activity of melatonin in advanced cancer patients. *Neuroendocrinol Lett.* 2001; **22**:45-7.
- 22 El-Domeiri AAH, Das Gupta TK. Reversal by melatonin of the effect of pinealectomy on tumor growth. *Cancer Res* 1973; **33**:2830-2833.

REFERENCES

- 1 Lissoni P, Viviani S, Bajetta E, et al. A clinical study of the pineal gland activity in oncologic patients. *Cancer* 1986; **57**:837-842.
- 2 Lissoni P. The pineal gland as a central regulator of cytokine network. *Neuroendocrinol Lett* 1999; **20**:343-349.
- 3 Regelson W, Pierpaoli W. Melatonin: a rediscovered antitumor hormone? *Cancer Invest* 1987; **5**:379-385.
- 4 Brzezinski A. Melatonin in humans. *N Engl J Med* 1997; **336**:186-195.
- 5 Lapin V, Frowein A. Effects of growing tumors on pineal melatonin levels in male rats. *J Neural Transm* 1981; **52**:123-126.
- 6 Bartsch H, Bartsch C. Effect of melatonin on experimental tumors under different photoperiods and times of administration. *J Neural Transm* 1981; **52**:269-279.
- 7 Anisimov VN, Poppovich IG, Zabezhinski MA. Melatonin and colon carcinogenesis. *Carcinogenesis* 1997; **18**:1549-1553.
- 8 Vijayalaxmi C, Thomas CR, Reiter RJ, Herman TS. Melatonin: from basic research to cancer treatment clinics. *J Clin Oncol* 2002; **20**:2575-2601.
- 9 Prozialeck WC, Boehme DH, Vogel WH. The fluorometric determination of 5-methoxytryptamine in mammalian tissues and fluids. *J Neurochem* 1978; **30**:1471-1475.
- 10 Beck O, Jonsson G, Lundman A. 5-methoxyindoles in pineal gland of cow, pig, sheep and rat. *P Pharmacol* 1981; **318**:49-52.