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Clinical Effects of the Pineal Antitumor and Psychedelic Beta-Carboline Pinealine in the Palliative Therapy of Untreatable Metastatic Cancer Patients

Giuseppe Di Fede[1], Giusy Messina[2]*, Alejandra Monzon[1], Ornella Meli[1], Carlo Gavazzeni[1], Franco Rovelli[1] and Paolo Lissoni[2]

[1]Institute of Biological Medicine, Milan, Italy
[2]International Institute of Clinical Psychoneuroendocrinoimmunology, Milan, Italy

***Corresponding author: Giusy Messina**,
Email: giusy.messina@libero.it

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Abstract

The pineal gland has been proven to play a fundamental role in mediating the influence of the psychospiritual status on the clinical course of the neoplastic diseases. Melatonin (MLT), the most investigated pineal hormone, has appeared to play an anticancer activity by either exerting a direct cytotoxic action or a stimulation of the anticancer immunity. However, MLT would not be the only hormone responsible for the anticancer role of the pineal gland. Other pineal indole hormones, such as the 5-methoxytryptamine (5-MTT), may have anticancer activity. More recently the pineal gland has been shown to represent the main source of beta-carbolines, which may exert both psychotropic and anticancer effects. The main endogenous beta-carboline would consist of the 6-methoxy-1,2,3,4-tetrahydro-beta-carboline, also called pinealine. High-dose of MLT alone or in association with 5-MTT may induce a disease control also in patients with disseminated cancer, and for whom no other standard antitumor treatment was available. This preliminary study was performed to evaluate the effects of a concomitant association of pinealine to high-dose MLT plus 5-MTT in a group of untreatable metastatic solid tumor patients. The study included 14 consecutive patients, who were treated orally with MLT al 100 mg/day in the night, 5-MTT at 5 mg/day at noon and pinealine at 1 mg/day in the evening. According to WHO criteria, the clinical response consisted of partial response (PR) in 1/14 (7%) and a stable disease (SD) in other 9 patients. Then, a disease control (PR + SD) was achieved in 10/14 (72%) patients, whereas the remaining 4 patients had a rapid progressive disease (PD). No pinealine-related biological toxicity occurred. Moreover, no hallucinatory phenomenon or anxiety exacerbation was observed with pinealine, at least at the employed dose of 1 mg/day. On the contrary, most patients referred a rapid improvement of mood. Moreover, 9 patients experienced also a clear well-being, due to an expansion of their self-consciousness and pleasure perception. This preliminary study shows that the pineal beta-carboline pinealine may rapidly improve mood and self-consciousness in patients with disseminated cancer, form whom no other standard anticancer therapy may be available. Therefore, pinealine could be successfully included within the common drugs used in the palliative therapy of cancer. On the other hand, as far as the potential anticancer activity of pinealine is concerned, these preliminary results seem to suggest that the association of pinealine may allow a percentage of disease control superior to that reported with the only pineal indoles. Further randomized studies, however, with the only pineal indoles or with pineal indoles plus pinealine will be required to establish whether the association of pinealine may further enhance the therapeutic antitumor activity already exerted by the pineal indoles.

Keywords: Beta-carbolines; Melatonin; Palliative therapy; Pineal gland; Pinealine

Introduction

It is an existential evidence, but also confirmed by the recent discoveries in tumor psychoneuroendocrinoimmunology (PNEI) [1], that all life conditions of open mind, including spiritual meditation, sexual excitation and amplification of pleasure [2], may play an anticancer activity by either inhibiting tumore cell proliferation, or stimulating the natural immunbiological resistance against cancer development. This is true also for all chemical agents able to expand the consciousness status, such as cannabinoids [3], pineal indole hormones [4] and beta-carbolines [5]. In contrast, all psychological conditions characterized by a decreased consciousness state [2], including stress, anxiety, depression, psychological conflicts and unconscious self-punishment situations, as well as chemical agents reducing the status of consciousness, namely mu-opioid agonists, may promote cancer growth by directly stimulating cancer cell proliferation [6]. This could result also through an inhibition of the antitumor immunity, mainly due to a stimulation of regulatory T lymphocytes (T reg) [7], which in contrast suppress the antitumor immune reaction [8]. The recent advances in the knowledge of tumor PNEI have allowed to identify the neurochemical mechanisms involved in mediating the influence of the emotions and the spiritual sensibility on the anticancer immunity [1,2], which is mainly induced by IL-2 [9] and IL-12 [10] and inhibited by TGF-beta released by T reg lymphocytes [11]. To synthetize, stress and depression would inhibit the anticancer immunity mainly through an activation of brain opioid system, whereas spirituality and pleasure would stimulate the anticancer immunity by activating the pineal-brain cannabinoid system functional axis [1-7]. On these bases, it becomes potentially possible to activate the anticancer immunity by acting not only on immune system itself, but also on its physiological psychoneuroendocrine modulation. In fact, from this point of view, it is known since more than 50 years that the pineal gland plays a fundamental role in determining the natural resistance against cancer growth [12,13]. This, by either inhibiting cancer cells proliferation [12], or stimulating the IL-2 and IL-12-dependent anticancer immunity [13] through the release of its most investigated indole hormone, melatonin (MLT) [14] and other less studied antitumor molecules [15,16], namely the indole 5-methoxy-tryptamine (5-MTT) [15] and various beta-carbolines, the most known of them is the 6-methoxy- 1,2,3,4-tetrahydro-beta-carboline, also called pinoline or pinealine (PNL) [16]. Melatonin, also known as *N*-acetyl-5-methoxy tryptamine, is a hormone produced by the pineal gland in animals, known as an antioxidant, regulator of sleep and wakefulness and with immunomodulating properties. Pinoline (6-methoxy-1,2,3,4-tetrahydro-β-carboline, usually abbreviated as 6-MeO-THBC). 5-Methoxytryptamine (5-MT) is a tryptamine derivative closely related to the neurotransmitters serotonin and melatonin. 5-MT has been shown to occur naturally in the body in low levels. It is produced by O-metilation of the neurotransmitter N-acetylserotonine by the enzime 5-hydroxyindole-O-methyltransferase (5-HIOMT), essential enzime in the biosyntethic pathway of Melatonin. The biological activity of this molecule is of interest as an antioxidant, and as a monoamine oxidase A inhibitor. The formation of pinoline requires 5-Methoxytryptamine as substrate, therefore endogenous synthesis of it is largely present in the pineal gland. Recent studies have also highlighted the antioxidant action and of free radical scavenger of melatonin and pinealine [17,18]. The pineal gland would constitute the main brain source of beta-carbolines, which originate from the condensation of indole-ethylamines and aldehydes and which may exert both antitumor effects and psychedelic expansion of mind [19], by playing a fundamental role in self-consciousness processes and in the chemistry of the spiritual

life, as suggested by the fact that the chemical principles of the main psychotropic plants are beta-carbolines, such as harmine and harmaline [20]. Moreover, beta-carbolines may induce antidepressant effects because of their inhibitory activity on MAO system [16-20]. Unfortunately, the psychopharmacology has been substantially applied until now only to act on the psychological life by influencing emotions and mood, or to control hallucinatory phenomenons, rather than to directly act on the consciousness status, in an attempt to induce or to restablish the condition of self-consciousness in patients with self consciousness deficiency, such as in autism and schizophrenia. At present, beta-carbolines are probably the less studied molecules of human body. In any case, the great difficulty to understand the effects of beta-carbolines would be due to their different molecular structure and to their modulatory activity on most neurotransmitters, including serotonin, dopamine, noradrenaline and Gaba-A, as well as to their interaction with benzodiazepine receptor [16-20]. Moreover, because of their potential amplification of self-consciousness and pleasure perception [16-20], it is probable that beta-carbolines may interact with brain cannabinoid system and with the mirror-neurons. They could constitute the main target for beta-carbolines, since they play an essential role in the mental processes of learning and self-consciousness [21], even though at present it is still unknown which may be the main neurotransmitter and cell surface receptor of mirror-neurons. Finally, the existence of specific receptors for beta-carbolines cannot be excluded. On the contrary, the mechanisms of the anticancer action of beta-carbolines have been well established, and they include both cytotoxic effects, consisting of an inhibition of topoisomerase-I, cyclin-dependent kinase and polo-like-kinase (PLK) activities, as well as an anti-angiogenic activity. The immunomodulatory effects of beta-carbolines have been less investigated. However, it is probable that they may stimulate the anticancer immunity because of their inhibitory activity on the production of TNF-alpha and PGE2 [22], which may suppress IL-2-dependent anticancer immunity [23]. Nevertheless, despite these experimental evidences, few studies only have been performed up to now in an attempt to evaluate the therapeutic effects of the endogenous anticancer molecules, such as pineal indoles and beta-carbolines, in untreatable disseminated cancer patients, at least in terms of palliative therapy. In any case, previous preliminary studies have already shown that pharmacological doses of MLT alone or in association with other pineal indoles may improve the clinical status and the survival time of metastatic cancer patients, for whom no other effective conventional therapy was available [24,25]. This is by counteracting some cancer-related symptoms, including cachexia, asthenia and depression, without any important biological toxicity. Some benefits in terms of reduction of disseminated cancer- related anxiety and depression have been also described with psychedelic agents, such as psylocibin [26], without, however, any apparent impact on the clinical course of the neoplastic disease. The present preliminary study was performed to evaluate whether the concomitant administration of PNL may further improve the clinical benefits, which may be achieved by MLT and other pineal indoles in untreatable metastatic cancer patients.

Patients & Methods

The study included 14 consecutive untreatable metastatic solid tumor patients, because of lack of response to previous chemotherapies. Eligibility criteria were, as follows: histologically proven metastatic solid tumor, measurable lesions, no availability of other standard anticancer therapies and life expectancy less than 6 months. Tumor histotype were, as follows: colon cancer: 2; breast cancer: 2; pancreatic adenocarcinoma: 2; endometrial adenocarcinoma: 2; small cell lung cancer: 1; hepatocarcinoma: 1; gastric cancer: 1; malignant melanoma: 1; thymic carcinoma: 1; germinoma: 1. Dominant metastasis sites were lung in 6, peritoneum in 3, liver in 2, lung plus peritoneum in 1, brain in 1, and bone in the last patient. Moreover, one patient with pineal germinoma was in comatous status following brain hemorrhagic episode. The major cancer progression-related symptoms consisted of asthenia in 8/14 patients, depression in 5 and cachexia in 6 patients. According to previous clinical studies [24-26], MLT and 5-MTT were given orally at 100 mg in the dark period and at 5 mg in the light period, respectively, corresponding to the daily periods of their maximal circadian production. In addition, PNL was also orally administered at a dose of 1 mg at the beginning of the dark period. Dose of PNL and time of administration were established on the basis of the results obtained in a group of healthy volunteers (unpublished data), consisting of amplification of self-consciousness and the capacity of mental attention, mood improvement, feeling of body perfection, amplification of pleasure perception, relief of asthenia and abolishment of the sedative effects due to alcohol assumption. The subjective effects of PNL rapidly appeared within 30 minutes after its administration and persisted for about 3 hours. The supportive therapy included also the administration of some potential antitumor plants, consisting of Aloe arborescens, Myrrh and Magnolia. The clinical response was assessed by WHO criteria, and data were statistically analyzed by the chi-square test.

Results

The clinical response consisted of partial response (PR) in 1/14 (7%) patients, who was affected by lung metastases due to breast cancer. A stable disease (SD) was achieved in other 9/14 patients. Then, a disease control (DC) (PR + SD) was obtained in 10/14 (72%) patients, whereas the remaining 4/14 (28%) patients had a progressive disease (PD). The results are reported in Table 1. As far as the subjective effects are concerned, an improvement in mood rapidly occurred within few days in 4/5 (80%) depressed patients. A relief of asthenia was achieved in 3/8 (37%) patients. Moreover, a control of weight loss was obtained in 4/6 (66%) patients with cachexia syndrome. Other subjective effects consisted of amplification of self-consciousness in 5/14 (36%) and enhanced perception of pleasure in 4/14 (28%) patients. An initial improvement in the status of consciousness was observed also in the patient, who was in comatous status. A transient exacerbation of anxiety for few days was seen only in one patient. Finally, two patients referred also initial phenomenons of extra-sensorial sensitivity. On the contrary, no subjective benefit, neither on mood, nor on asthenia, was observed in the 4 patients, who had a PD. Then, the percentage of improvement in the clinical status and in self-consciousness achieved in patients with objective tumor regression or SD was significantly higher than that found in patients with PD (6/10 vs 0/4, $P < 0.05$). No cardiac, haematological, neurological, renal and hepatic toxicity occurred.

Discussion

This preliminary study, carried out to explore the potential therapeutic

Table 1: Clinical response (WHO criteria) in 14 untreatable metastatic cancer patients.

CLINICAL RESPONSE*							
PATIENTS	N.	CR	PR	CR+PR	SD	DC	PD
OVERALL PATIENTS	14	0	1 (7%)	1	9	10 (72%)	4 (28%)
IMPROVEMENT IN THE CLINICAL STATUS						6 (60%)**	0 (0%)

*CR: complete response; PR: partial response; SD: stable disease; DC (CR+PR+SD): disease control; PD: progressive disease.
**P<0.05 vs patient with PD

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benefits of the endogenous beta-carbolines in the palliative therapy of human neoplasms within a psychoneuroendocrine approach to cancer cure, would show that the pineal beta-carboline PNL is a well tolerated therapy, which may be administered also to patients with poor clinical conditions. With respect to other previous psychoneuroendocrine combinations with the only pineal antitumor indoles [24,25], the results of the study seem to suggest that the association of PNL would further improve the already described subjective benefits obtained with the only pineal indoles, particularly in the control of depression, asthenia and cachexia. The results achieved in terms of disease stabilization would also seem to be superior to those reported with the only pineal indoles, which may determine a control of the neoplastic growth in a percentage generally less than 50%. Successive randomized studies, however, of pineal indole therapy with or without a concomitant PNL administration will be needed to establish whether PNL may allow better results also in terms of disease control with respect to an antitumor psychoneuroendocrine regimen consisting of the only pineal hormones, whose anticancer properties are known since many years. In any case, the administration of PNL to patients with disseminated cancer could constitute a substitutive therapy of cancer-related pineal deficiency. In fact, since pineal histological damages have been described in patients died from cancer [27], it is probable that cancer-related pineal endocrine deficiency does not regard the only secretion of MLT, as commonly considered [4,12]. It might involve the whole pineal function instead, including the secretion of indoles other than MLT and of beta-carbolines themselves, even though the studies concerning the pineal function in cancer patients are limited to the only MLT secretion, since there are no data about that of beta-carbolines and other pineal indoles. Moreover, further studies will be required to better define the mechanisms involved in the psychotropic action of beta-carbolines. According to the knowledgements available up to now, the well-being effects induced by beta-carbolines would be due to their modulatory activity on the neurotransmission pathways. In more detail, the relief of asthenia and mood improvement could be due to a stimulation of the noradrenergic and serotoninergic transmissions, respectively. The amplification of self-consciousness, extra-sensorial sensitivity and pleasure perception instead would depend on a stimulation of dopaminergic transmission and on possible interactions with brain cannabinergic system and mirror-neurons.

These preliminary studies warrant further randomized studies only with pineal indole hormones or with pineal indole hormones plus melatonin to confirm the results. In addition, further studies will be necessary to determine which tumor histology is more responsive to treatment with pineal indole hormones.

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