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ORIGINAL ARTICLE

Oncostatic activity of pineal neuroendocrine treatment with the pineal indoles melatonin and 5-methoxytryptamine in untreatable metastatic cancer patients progressing on melatonin alone

Paolo Lissoni,[1] Franco Rovelli,[1] Andrea Frassineti,[1] Luca Fumagalli,[1] Ola Malysheva,[2] Ario Conti[3] & Georges Maestroni[3]

1. Division of Radiation Oncology, S.Gerardo Hospital, Monza (Milan), Italy.
2. Institute of Clinical Immunology, Russian Academy of Medical Sciences, Novosibirsk, Russia.
3. Institute of Pathology, Locarno, Switzerland.

Correspondence to: Dr Paolo Lissoni,
Divisione di Radioterapia Oncologica, Ospedale S.Gerardo,
20052 Monza (Milan), Italy.
FAX +39 039 233 3414

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Abstract

OBJECTIVE: The recent advances in psycho-neuro-endocrino-immunology have demonstrated the existence of several endogenous neuroendocrine substances, capable of affecting both tumor growth and host anticancer immune defenses. The pineal gland would represent one of the most important organs releasing antiproliferative and immunostimulating substances, the most known of them is melatonin (MLT). However, MLT would not be the only pineal indole provided by antitumor activity. Other pineal indoles, namely 5-methoxytryptamine (5-MTT), would play antitumor effects, by either inhibiting cancer cell proliferation or stimulating the anticancer immunity. Preliminary data have shown that MLT may deserve antitumor activity in the treatment of human neoplasms, whereas at present there are no clear data about 5-MTT. In an attempt to obtain some preliminary data about the anticancer properties of 5-MTT in humans, we have evaluated the efficacy of MLT plus 5-MTT in untreatable advanced cancer patients progressing on MLT alone. METHODS: The study included 73 untreatable advanced solid tumor patients, who had progressed after two months of MLT therapy alone. According to tumor histotype, patients were randomized to receive MLT alone (20 mg/day orally in the evening) or MLT plus 5-MTT (1 mg at noon orally), every day for at least two months. The clinical response was evaluated according to WHO criteria. RESULTS: A partial response (PR) occurred in two patients treated with MLT + 5-MTT and in none of the patients receiving MLT alone. A stable disease (SD) was achieved in only 2/37 patients on MLT therapy alone, and in 8/36 patients receiving MLT plus 5-MTT. Therefore, the percent of non-progressing patients (SD + PR) obtained with MLT plus 5-MTT was significantly higher than that obtained with MLT alone. Moreover, the relief of asthenia and depressant symptoms was significantly higher in patients concomitantly treated with 5-MTT. DISCUSSION: This preliminary study would suggest that the concomitant administration of the less known pineal indole 5-MTT, also provided by antiproliferative and immunomodulating effects, may further amplify the oncostatic activity of the pineal hormone MLT in the palliative and curative therapy of advanced untreatable human solid neoplasms.

Introduction

The pineal gland is one of the most important antitumor organs, responsible for the natural resistance against tumor onset and dissemination [1]. In fact, every type of anatomic or functional damage of the pineal gland, including pinealectomy itself [2], exposure to magnetic fields [3] and depression-related hypopinealism [4], has been proven to be associated with enhanced tumor frequency. In contrast, the conditions characterized by hyperfunction of the pineal gland, such as blindness, have appeared to be associated with reduced tumor incidence [5]. Finally, the evidence of pineal degenerations is typical of the advanced neoplastic disease [6].

Despite the demonstration of several antitumor pineal substances [1, 7], at present almost all experimental and clinical studies on the antitumor properties of the pineal gland have been limited to the most known pineal hormone, melatonin (MLT) [7–10]. According to the knowledge confirmed by several experiments, it has been demonstrated that the anticancer activity of pineal MLT depends on at least five different molecular mechanisms: 1) direct antiproliferative effect on cancer cell lines expressing MLT receptors; 2) anti-oxidant activity, with a following protection against further cellular genetic damages; 3) inhibition of tumor growth factor production; 4) stimulation of cancer cell differentiation by modulating endocrine receptor, oncogene and anti-oncogene expression; 5) immunomodulating activity, namely consisting of stimulation of the release of the two major anticancer cytokines in humans, IL-2 [11] and IL-12 [12].

The administration of MLT has been proven to reverse, but not completely abrogate, the promoting effect of pinealectomy on cancer cell growth and dissemination [1]. This finding would suggest that MLT is not the only antitumor substance released from the pineal gland. In fact, other pineal indoles [13] and less characterized pineal peptides [7] may play anticancer activity. In particular, within the indole hormone group, the pineal indole 5-methoxytryptamine (5-MTT) would seem to deserve promising anticancer properties [13]. In fact, 5-MTT has been proven in vitro to play antiproliferative effects on cancer cell proliferation superior than those of MLT itself [13]. However, at present it is still unknown whether the antiproliferative activity may constitute the only mechanism responsible for the potential anticancer property of 5-MTT, or whether it may play other biological actions, namely the activation of the anticancer immunity, as well as MLT itself. Recent data have shown that 5-MTT may also play antioxidant activity [14], which would be related to the 5-methoxylic group. Moreover, preliminary data would suggest that 5-MTT may also exert important immunomodulating effects on cytokine secretion, consisting of inhibition of tumor necrosis factor-alpha (TNF) secretion with following anti-cachectic property [15], and stimulation of Il-2 and gamma-interferon release with following antitumor immunomodulatory effects [16]. In more detail, 5-MTT would be more effective than MLT in activating the monocyte-macrophage system in an antitumor way, whereas MLT would be more effective on lymphocytes [16]. 5-MTT modulation of macrophages could deserve important clinical applications in the biotherapies of tumors, since in physiopathological conditions macrophages would exert a dominant suppressive effect on host anticancer immune defense rather than to stimulate the anticancer immunity [17].

MLT nocturnal production has appeared to progressively decline with tumor progression [18], with a following progressive disappearance of the physiological light/dark rhythm of the pineal indole [19]. In contrast, at present there are no data about 5MTT secretion in cancer patients. However, preliminary data would suggest that MLT deficiency tends to be associated with diminished production of other pineal indoles [20]. Therefore, it is probable that the neoplastic disease may be characterized by deficiencies of the overall pineal indoles, as also suggested by the anatomopathological evidence of cancer progression-related pineal damage [6]. Finally, MLT has been proven to be effective at least in the palliative treatment of untreatable metastatic cancer patients [21, 22], with stabilization of the neoplastic growth in about 20% of patients, for whom no other effective standard antitumor therapy is available. In contrast, at present there are no data about the possible efficacy of 5-MTT as a neuroendocrine therapy of tumors. The present study was performed to evaluate the antitumor activity of MLT-5-MTT association in untreatable advanced cancer patients progressing on MLT alone, in an attempt to establish whether the concomitant administration of 5-MTT may further amplify the oncostatic activity of MLT.

Materials and methods

Eligibility criteria were, as follows: histologically proven advanced solid neoplasms, measurable lesions, lack of response to previous standard chemotherapies or poor clinical conditions, which make patients as unable to tolerate the conventional polychemotherapies, no double neoplasm, no concomitant chronic therapy with steroids or other drugs inhibiting the immune functions, and progression on a previous neuroendocrine therapy with MLT alone.

MLT was supplied by Helsinn Chemicals (Biasca, Switzerland), while 5-MTT was supplied by Sigma-Aldrich Chemie (Schnelldorf, Germany). The experimental protocol was explained to each patient, and informed consent was obtained. Moreover, the protocol was accepted by the Ethical Committee.

The study was performed in 73/100 untreatable advanced solid tumor patients, who progressed after months of treatment with MLT alone. The remaining 27 patients, who did not progress on MLT therapy, continued their therapy with only MLT. After stratification according to tumor histotype and disease extension, the 73 patients progressing on MLT alone were randomized to receive MLT plus 5-MTT or MLT alone. Both MLT and 5-MTT were administered orally every day, until disease progression. MLT was given during the dark period of the day in an attempt to reproduce its physiological light/dark circadian rhythm. 5-MTT was given during the period of maximum light to offset its possible transformation into MLT after acetylation by N-acetyltransferase (NAT), which is activated only during the dark period of the day [23]. The dose was 20 mg for MLT and 1 mg for 5-MTT daily, every day.

The clinical response was evaluated according to WHO criteria. Complete response (CR) and partial response (PR) were defined as a complete regression of all neoplastic lesions or as a reduction of at least 50% in the sum of the products of the longest perpendicular diameters, respectively, for at least one month. Stable disease (SD) was defined as no objective cancer regression or increase greater than 25% of the neoplastic lesions. Progressive disease (PD) was defined as an increase greater than 25% in measurable lesions or the appearance of the new lesions. The radiological examinations, including CT-scan, were done before the onset of treatment, after the first two months of treatment, and thereafter every three months. The performance status (PS) was evaluated according to the Karnofsky's score. Cachexia was defined as a weight loss greater at least than 10%. Improvement in the appetite and relief of asthenia and depressant symptoms were assessed by specific patient report.

Data were analysed by the chi-square test, and the Student's t-test, as appropriate.

Results

The clinical characteristics of the two groups of patients treated with MLT or MLT plus 5-MTT are reported in Table 1. As shown, the two groups of patients were well balanced for the overall main prognostic variables, including tumor histotype, dominant metastasis sites, PS and age. Distant organ metastases were present in all patients, except those with brain glioblastoma, who had a locally advanced disease.

Table 1. Clinical characteristics of untreatable metastatic solid tumor patients treated with melatonin (MLT) alone or MLT plus 5-methoxytryptamine (5-MTT).

CHARACTERISTICS	MLT	MLT+5-MTT
NUMBER	37	36
M/F	21/16	22/14
MEDIAN AGE (YEARS)	59 (45–74)	61 (43–75)
MEDIAN PERFORMANCE STATUS (KARNOFSKY)	70 (30–90)	70 (30–90)
TUMOR HISTOTYPES		
-LUNG CANCER	11	12
-Non-small cell carcinoma	8	10
-Small cell carcinoma	3	2
-COLORECTAL CANCER	6	5
-GASTRIC CANCER	3	2
-HEPATOCARCINOMA	4	5
-BILIARY TRACT CARCINOMA	2	2
-PANCREATIC CANCER	2	1
-PROSTATE CANCER	3	3
-BRAIN GLIOBLASTOMA	4	3
-BLADDER CANCER	1	2
-HEAD AND NECK CANCER	1	1
DOMINANT METASTASIS SITES		
-BONE	6	5
-LUNG	11	11
-LIVER	9	8
-LUNG+LIVER	7	9
PREVIOUS CHEMOTHERAPIES	30/37	28/36

No patient achieved a CR. A PR occurred in 2/36 (55%) patients treated with MLT plus 5-MTT (lung cancer: 1, colon cancer: 1) and in none of the patients who received MLT alone. SD occurred in 8/36 (22%) patients treated with MLT plus 5-MTT and in only 2/37 (5%) patients on MLT therapy alone. Therefore, the percent of non-progressing patients (PR+SD) was significantly higher in the group treated with MLT plus 5-MTT than in that undergoing MLT alone (10/36 vs. 2/37, $P<0.01$). The remaining 26/36 patients treated with MLT plus 5-MTT and 35/37 patients who received MLT alone had PD. No cachexia occurred in the patients of both groups. PS improved in 15/36 (42%) patients on MLT plus 5-MTT therapy and in 8/37 (22%) patients of MLT group. This difference was statistically significant ($P<0.05$). A clear relief of asthenia and depressant symptoms was achieved in 7/13 (54%) patients of MLT plus 5-MTT group and in only 2/15 (13%) patients of MLT group, who presented a pronounced asthenia prior to therapy. This difference was also statistically significant ($P<0.05$). In addition, a clear stimulation of the appetite occurred in 16/36 (44%) patients and in only 2/37 (5%) patients who received MLT alone ($P<0.01$). Table 2 shows the clinical response obtained in the two groups of patients in relation to tumor histotype. Non-small cell lung cancer, hepatocarcinoma, prostate cancer, colon cancer and brain glioblastoma were the tumors which obtained more benefit from the treatment with MLT plus 5-MTT. Finally, no MLT- or 5-MTT-related toxicity was observed. The subjective effects consisted of relaxation and sleepiness for MLT, and serenity and well-being for 5-MTT. From a biological point of view, mean lymphocyte increase observed after two months of treatment was higher in patients treated with MLT plus 5-MTT than in those who received MLT alone, even though the difference was not statistically significant (428 + 54 vs. 295 + 47/mm).

Discussion

This preliminary study, by showing a SD on pineal polyneuroendocrine therapy with MLT plus 5-MTT in untreatable metastatic solid tumor patients progressing on MLT alone, would suggest that the concomitant administration of 5-MTT may further amplify the oncostatic properties of MLT in human neoplasms. Obviously, this study does not allow us to establish whether the potentiation of the oncostatic activity obtained by associating 5-MTT may depend on its direct antiproliferative and immunomodulating activity, or whether it may mainly act by amplifying the efficacy of MLT itself. In particular, it is still unknown whether 5-MTT may act on specific receptors, or whether it may act by activating the well demonstrated melatoninergic receptors [24]. In any case, from a clinical therapeutic point of view, this preliminary study would suggest that 5-MTT may be more effective than MLT in the treatment of advanced cancer-related symptoms, namely asthenia and the absence of appetite. These palliative properties of 5-MTT are not surprising, since their evident psychomimetic activity

Table 2. Clinical response (WHO criteria*) in advanced solid tumor patients treated with melatonin (MLT) alone or MLT plus 5-methoxytryptamine (5-MTT)

	MLT					MLT+5-MTT				
HISTOTYPE	n	CR	PR	SD	PD	n	CR	PR	SD	PD
OVERALL TUMORS	37	0	0	2	35	36	0	2	8	26
-LUNG CANCER	11	0	0	1	10	12	0	1	2	9
-Non-small cell carcinoma	8	0	0	1	7	10	0	1	2	7
-Small cell carcinoma	3	0	0	0	3	2	0	0	0	2
-COLORECTAL CANCER	6	0	0	0	6	5	0	0	1	3
-GASTRIC CANCER	3	0	0	0	3	2	0	0	0	2
-HEPATOCARCINOMA	4	0	0	1	3	5	0	0	2	3
-BILIARY TRACT CARCINOMA	2	0	0	0	2	2	0	0	0	2
-PANCREATIC CANCER	2	0	0	0	2	1	0	0	0	1
-PROSTATE CANCER	3	0	0	0	3	3	0	0	1	2
-BRAIN GLIOBLASTOMA	4	0	0	0	4	3	0	0	1	1
-BLADDER CANCER	1	0	0	0	1	2	0	0	1	1
-HEAD AND NECK CANCER	1	0	0	0	1	1	0	0	0	1

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

has been confirmed by several experimental observations [25, 26]. In any case, further randomized studies with MLT alone versus 5-MTT alone will be required to better define the efficacy of the single pineal indoles in the curative or palliative treatment of metastatic cancer patients, for whom no other standard effective therapy may be available. Moreover, further studies will be required to establish which may be the optimal dose and timing of administration of 5-MTT itself. Finally, successive clinical investigations, by monitoring changes in the secretion of cytokines provided by antitumor activity, such as IL-2 and IL-12, or immunosuppressant action, such as IL-2 and IL-12, or immunosuppressant action, such as IL-6 and IL-10, will be necessary to better define the immunomodulatory properties of the pineal indoles.

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