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A Randomized Study of High-Dose Pineal Hormone Melatonin Alone Versus High-Dose Melatonin Plus Low-Dose Angiotensin-(1-7) in Untreatable Advanced Cancer Patients

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ABSTRACT

The recent advances in the knowledge of the neuroendocrine control of the immune system and cancer growth have demonstrated the existence of several anticancer natural molecules in the human body, the most promising of them are the pineal hormone melatonin (MLT) and the enzymatic product of ACE2, the angiotensin 1-7 (Ang 1-7). Both MLT and Ang 1-7 have no toxicity, and they exert their antitumor action through several mechanisms, including inhibition of cancer cell proliferation and angiogenesis, and stimulation of the anticancer immunity. Previous preliminary clinical studies had already shown that high-dose MLT may induce a disease control in advanced cancer patients eligible for the only palliative therapy. The present study was performed to evaluate whether the concomitant administration of Ang 1-7 may furtherly increase the antitumor efficacy of MLT in untreatable cancer patients suffering from various tumour histotypes. The study included 70 consecutive advanced untreatable cancer patients, who were randomized to receive the only best supportive care, high-dose MLT (100 mg/day in the dark period), or MLT plus Ang 1-7 (0.5 mg twice/day). The percentage of disease control (DC), including stable disease and tumor regressions, achieved in patients treated by MLT plus Ang 1-7 was significantly higher with respect to those obtained in patients treated with MLT alone ($P<0.05$) or with the only supportive care ($P<0.001$). No toxicity was seen under therapy of MLT plus Ang 1-7. In contrast, most patients experienced mood improvement, a diminished anxiety, and a relief of asthenia, which was more evident in patients concomitantly treated by MLT and Ang 1-7.

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Introduction

The knowledgements of tumour biology have demonstrated that cancer growth is under an immune and neuroendocrine regulation [1-5].The immune-mediated inhibition of cancer progression is mainly exerted by IL-2 and IL-12, which stimulate the antitumor cytotoxicity exerted by NK cells and by T cytotoxic lymphocytes, respectively [6,7]. In contrast, the anticancer immunity is suppressed by both macrophage-related inflammatory immunosuppressive cytokines, including IL-6 and TNF-alpha, and the anti-inflammatory immunosuppressive cytokines TGF-beta and IL-10, mainly released from regulatory T (T reg) lymphocytes [8]. More recently, IL-17 has been proven to play a major pro-tumoral role by directly stimulating both cancer cell proliferation and angiogenesis, despite its potential anti-tumor action due to its inhibitory effect of T reg cells, which stimulate cancer growth by suppressing the antitumor immunity [8-10]. On the other side, the neuroendocrine control of tumor progression is mainly mediated by the pineal gland and brain cannabinoid system [11,12].

The most investigated pineal hormone is melatonin (MLT), which plays an anticancer activity by either inhibiting cancer cell proliferation or stimulating IL-2-dependent anticancer immunity [11,13]. In any case, MLT, which is mainly produced during the dark period of the day, is not the only anticancer pineal hormone, since at least another pineal indole hormone has to be considered, the 5-methoxy-tryptamine (5-MTT), which in vitro has been proven to play an anticancer antiproliferative action superior to that of MLT itself [11,14]. On the same way, the cannabinoid agonists may counteract cancer growth by either exerting a cytotoxic anticancer and anti-angiogenic actions or inhibiting IL-17 secretion [12], which in contrast stimulates cancer cell proliferation and macrophage release of inflammatory suppressive cytokines, including IL-1beta, IL-6 and TNF-alpha [9,15,16].

Cancer growth may be also counteracted by the fatty acid amide hydrolase (FAAH) inhibitors, including the exogenous cannabidiol (CBD), the non-psychoactive molecule of Cannabis plant and the endogenous palmitoyl-ethanol-amide (PEA), which may allow an increased endogenous cannabinoid content by inhibiting FAAH activity, the enzyme involved in cannabinoid degradation, even

though they are not cannabinoid agonists [2,17-19]. On the contrary, the opioid agonists, mainly the mu-agonists ones, may exert a pro-tumoral activity by either suppressing the anticancer immunity or stimulating cancer cells proliferation [20,21]. In addition, another biological system has recently appeared to play an important role in the control of the immunoinflammatory biological response and cancer development, the ACE – ACE2 system [22].

Until few years ago, ACE – ACE2 system was thought to be involved in the only control of blood pressure and cardiovascular functions [23]. On the contrary, recent experiments have demonstrated the importance of ACE-ACE2 system in the regulation of the main biological functions, including inflammatory status, cell proliferation, age-related organ fibrosis and insulin resistance, through their products, which are respectively represented by angiotensin II (Ang II) and angiotensin 1-7 (Ang 1-7) [22-25]. Ang II and Ang 1-7 are characterized by opposite effects, by constituting respectively some of the main detrimental and regenerative molecules of human body. In fact, Ang II has appeared to exert hypertensive, inflammatory, pro-tumoral, pro-ischemic, pro-thrombotic and pro-fibrotic effects, whereas Ang 1-7 plays hypotensive, cardioprotective, anti-inflammatory, anti-tumoral, anti-ischemic, anti-thrombotic and anti-fibrotic effects.

Therefore, ACE 2, by transforming Ang II into Ang 1-7, not only neutralizes the negative toxic effects of Ang II, but it produces a regenerative molecule, such as Ang 1-7, by representing a real biological miracle.

Moreover, ACE – ACE2 system has appeared to be under a neuroimmune regulation, mainly played by IL-17 and MLT, with opposite effects. In fact, IL-17 has been proven to stimulate ACE expression and to inhibit that of ACE2, whereas MLT inhibits ACE expression and consequently promotes that of ACE2 with a following enhanced Ang 1-7 production [26-27]. Ang 1-7, produced by the action of ACE2, has been proven to exert an anticancer action in both experimental and clinical conditions by either inhibiting cancer cell proliferation or counteracting cancer-related inflammatory status (24,25,28) mediated by an hyperactivation of the macrophage system [24,25,28,29].

High-dose MLT alone or in association with other pineal anticancer hormones has appeared to prolong the survival time in disseminated cancer patients, who progressed under the conventional anticancer therapies and for whom no other effective standard therapy was available [30,31]. On the contrary, the clinical employment of cannabinoid agents in the curative treatment of cancer is still at the beginning because of their use for the only palliative therapy of tumours [12,17,32]. Finally, the employment of ACE2 and its active product Ang 1-7 is still at the beginning. In any case, preliminary studies have already shown that Ang 1-7 at doses ranging about from 1 to 5 mg/day or more has been proven to counteract cancer growth, to inhibit the inflammatory response, to opposite the fibrotic processes induced by both age and chronic inflammation, and to reduce the insulin resistance, in addition to its most known hypotensive and cardiovascular protective effects, with potential therapeutic effects in the treatment of hypertension, pulmonary arterial hypertension and both cardiac and brain ischemic diseases [23-25, 33-37]. In addition, very preliminary clinical results have shown that Ang 1-7 may prevent the haematological toxicity of cancer chemotherapy, including lymphopenia and thrombocytopenia [38].

Finally, Ang 1-7 has also appeared to reduce cancer-induced bone pain [39]. The therapeutic actions of ACE2 are mediated by Ang1-7 itself, because of the administration of Ang 1-7 antagonists has appeared to abrogate the therapeutic effects of ACE2 itself [40]. The planetary infection of Covid19 has furtherly demonstrated the fundamental role of ACE2 in the regulation of host inflammatory response [39]. In fact, it has been shown the link of COVID19 spike protein to ACE2 receptor does not allow the only viral entry into the cells, but also a down-regulation of ACE2 expression, with a following decline in Ang 1-7 production and consequent exaggerated inflammatory reaction, mediated by IL-6, TNF-alpha, and IL-17, which would constitute the main cytokine involved in Covid19-induced severe acute respiratory syndrome (SARS), because of its further inhibitory action on ACE2 expression [26,41].

As far as the neoplastic diseases are concerned, the anticancer action of Ang 1-7 is mainly due to its antiproliferative and anti-angiogenic properties, while its effects on the anticancer immunity need to be furtherly investigated, even though it has been shown that Ang 1-7 may inhibit the monocyte-macrophage system, which plays a major pro-tumoral role on cancer growth [29,33,38,41,42]. In fact, the evidence of a progressive decrease in lymphocyte-to-monocyte ratio (LMR), due to a decline in lymphocyte count and/or to an increase in monocyte number, has appeared to predict a poor prognosis and a lower survival in advanced cancer patients, since cancer growth is mainly counteracted by lymphocytes and promoted by the macrophage system, whose activation has been shown to correlated with monocyte count [29,43,44].

Therefore, the association of Ang 1-7 could amplify the antitumor immunomodulating properties of MLT itself by decreasing monocyte count, while MLT mainly acts by enhancing lymphocyte number through a stimulation of IL-2 production from Th 1 cells, the main growth factor for lymphocytes. Moreover, Ang 1-7 has also appeared to counteract cancer progression-related and chemotherapy-induced thrombocytopenia and lymphopenia [13,38,42]. On these bases, a randomized study was planned in untreatable advanced cancer patients with high-dose MLT alone or MLT plus low-dose Ang 1-7 to evaluate whether the association of Ang 1-7 may furtherly improve the clinical benefit induced by high-dose MLT, as previously already reported in the literature in terms of both disease stabilization and improvement in LMR [11,30,31].

Materials and Methods

The study included 70 consecutive advanced cancer patients eligible for the only supportive care, because of lack of response to the previous standard anticancer treatments. Patients were randomized to receive the only best supportive care, high-dose MLT alone or high-dose MLT in association with Ang 1-7. Eligible criteria were, as follows: histologically proven advanced or metastatic solid tumours, measurable lesions, and lack of response or progression under the conventional anticancer therapies, including chemotherapy, endocrine therapy, immunotherapy, and targeted therapy, then for whom there was no availability of further standard antitumor treatments. After the approval of the Ethical Committee, the experimental protocol was explained to each patient, and written consent was obtained. Then, according to tumour histotype and disease extension, patients were randomized to receive the only palliative therapy as a control group, high-dose MLT alone, or MLT plus Ang1-7.

MLT was given orally at a dose of 100 mg/day during the dark period of the day according to its physiological circadian rhythm, every day without interruption. Ang 1-7 was also given orally

in gastro-protected capsules at a dose of 0.5 mg twice/day. We decided to use Ang 1-7 at a minimal dose because of the possible promoting effect of MLT on ACE2 expression and consequently on Ang 1-7 production [27]. Radiological examinations, including TC, NMR and PET, were made prior to therapy and at 3-month intervals. The clinical response was assessed according to WHO criteria. Lymphocyte, monocyte counts and LMR were evaluated prior to therapy and at 10 days intervals. Normal values of LMR observed in our laboratory (95% confidence limits) was greater than 2.1. Data were reported by mean +/- SE, and statistically analysed by the chi-square test, the Student's t test, and ANOVA method, as appropriate.

Results

The characteristics of patients and their clinical response evaluated after 3 months of therapyare reported in Table 1. No complete response (CR) occurred. However, a partial response (PR) was seen in 3/24 (13%) patients treated with MLT plus Ang 1-7, in 1/23 (5%) patients treated with MLT, and in none of the patients, who received the only palliative therapy. A stable disease (SD) was obtained in 15/24 (63%) patients treated by MLT and Ang 1-7, in 12/23 (52%) patients treated by MLT alone, and in only 3/23 (13%) of patients treated with the only palliative therapy. Then, the percentage of disease control (DC) (PR+SD) achieved in patients concomitantly treated with MLT and Ang1-7 was significantly higher with respect to those obtained with MLT alone ($p<0.05$) or with the only palliative therapy ($p<0.001$). No toxicity occurred under therapy with MLT alone or MLT plus Ang 1-7, and particularly no important decline in blood pressure was observed. On the contrary, most patients experienced mood improvement, decreased anxiety, and relief of asthenia, whose percentage was significantly higher in patients who received MLT plus Ang 1-7 than in those treated by MLT alone (17/24(71%) vs 9/23 (39%), $P<0.01$). Abnormally low values of LMR less than 2.1 were seen prior to therapy in 38/70 (54%) patients, without differences in relation to the type of therapy (control group: 13/23(57%); MLT group: 12/23 (57%); MLT plus Ang 1-7 group: 13/24 (54%). A normalization of LMR was obtained within the first 3 months of therapy in 7/12 (58%) patients treated with MLT alone, in 9/13 (69%) patients treated with MLT plus Ang 1-7, and in none of the patients, who received the only palliative therapy. This difference was statistically significant ($P<0.001$).

Discussion

The results of this clinical study, which has been carried out in advanced cancer patients for whom no other standard anticancer therapy was available, show that high-dose MLT may counteract cancer growth and induce a disease stabilization in a percentage of cases significantly higher with respect to that spontaneously occurring under the only palliative therapy, according to previous preliminary results [30,31,33]. Moreover, this study shows for the first time that the concomitant administration of Ang 1-7, whose antitumor activity has been well documented, may furtherly increase the clinical anticancer efficacy of MLT [22-24]. This finding is not surprising, since MLT and Ang 1-7 have appeared to be connected by several reciprocal promoting effects in the inhibitory control of both inflammatory response and cancer growth [4,27,33]. Moreover, the association between LMR increase and disease control observed in the present study would suggest that the inhibitory action of MLT and Ang 1-7 on cancer growth may be at least in part mediated by a stimulation of the anticancer immunity.

Unfortunately, most complementary medicines employed in the treatment of cancer use potential antitumor molecules drawn from plants and mushrooms. On the contrary, this study would suggest that the main natural anticancer molecules may be researched within human body itself, such as MLT and Ang1-7. In any case, further studies will be required to define the efficacy of Ang 1-7 in relation to its dosage, since in the present study Ang 1-7 has been employed at a low dose. Moreover, further clinical studies with MLT plus Ang 1-7 in a greater number of patients affected by different tumour histotypes will be needed to establish which may be the histotypes of cancer, which could achieve more benefits from this neuroendocrine antitumor regimen. Finally, successive studies by monitoring changes in the blood concentrations of the different cytokines, mainly those of IL-17 and TGF-beta, will be necessary to establish the importance of changes in the different cytokine secretions in influencing the anticancer efficacy of treatment.

Table 1: Clinical characteristic of untreatable solid tumour patients treated with melatonin (MLT) alone, MLT plus angiotensin 1-7 (Ang 1-7), or with the only palliative therapy as a control group, and their clinical response (WHO criteria).

PATIENTS	CONTROLS	MLT	MLT +Ang 1-7
N	23	23	24
M/F	12/11	13/10	11/13
Median age (years)	59 (38-73)	62 (36-82)	61 (5-83)
TUMOR HISTOTYPES			
- Brain glioblastoma	4	5	5
- Colorectal cancer	4	4	5
- Pancreatic cancer	2	2	2
- Biliary tract cancer	1	2	1
- Gastric cancer	1	0	1
- Non-small cell lung cancer	2	2	2
- Breast cancer	1	2	2
- Sarcoma	1	0	2
- Gynaecologic tumours	3	2	1
- Renal cancer	1	1	1
- Prostate cancer	1	1	0
- Melanoma	1	1	0
- Neuroendocrine tumour	1	1	1
- Pharynx carcinoma	0	0	1
METASTATIC DISEASE	19/23 (83%)	18/23 (78%)	18/24 (75%)
DOMINANT METASTASIS SITES			
- Soft tissues and nodes	2	3	2
- Bone	1	0	1
- Lung	4	5	4
- Liver	8	6	6
- Lung plus liver	1	0	0
- Peritoneum	2	1	2
- Brain	1	3	3
CLINICAL RESPONSE			
- Complete response (CR)	0	0	0
- Partial response (PR)	0	1	3
- Tumor regression (CR+PR)	0	1/23(5%)	3/24 (13%)
- Stable disease(SD)	3/23 (13%)	12/23(52%)	15/24 (63%)
- Disease control (CR+PR+SD)	3/23(13%)	13/23 (57%)**	18/24(75%)*
- Progressive disease (PD)	20/23 (87%)	10/23 (43%)	6/24 (25%)

*P<0.05 vs MLT alone, P<0.001 vs controls; **P<0.001 vs controls

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