ORIGINAL ARTICLE

The Neuroendocrine Regimen with Melatonin Plus Angiotensin 1-7 Improves the Survival Time in Untreatable Advanced Solid Tumor Cancer Patients

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ABSTRACT

Recent researches have shown that human body may produce several anticancer non-toxic molecules, the most investigated of them are represented by the pineal hormone melatonin (MLT), the product of ACE2 angiotensin 1-7 (Ang 1-7), and the endogenous cannabinoids. Despite this evidence, almost all complementary medicines of cancer are limited to the use of natural vegetal antitumor factors rather than the same human anticancer molecules. MLT has been already shown to control cancer growth also in cancer patients, who failed to respond to the standard anticancer treatments. Moreover, preliminary studies seem to suggest that the antitumor activity of MLT may be amplified by a concomitant administration of the other endogenous major anticancer hormone, the Ang 1-7. On these bases, a randomized study was planned with the only palliative therapy, high-dose MLT, or high-dose MLT plus low-dose Ang 1-7 in 60 advanced solid tumor patients, who did not respond the standard anticancer therapies, and life expectancy less than 1-year. Both MLT and Ang 1-7 were given orally, respectively at 100 g/day in the evening and at 1 mg/day in the morning. Only 1/20 (5%) patients treated with the only palliative therapy was alive at 1 year. Both treatments with MLT alone or MLT plus Ang 1-7 allowed a significant increase in the survival time ($P<0.001$), and the percent of 1-year survival achieved in patients concomitantly treated with MLT plus Ang 1-7 was significantly higher with respect to that observed with MLT alone (17/21 (81%) vs 9/19 (47%), $P<0,05$). Neither MLT, nor Ang 1-7-related toxicity occurred. On the contrary, most patients experienced an improvement in mood and asthenia, particularly in those treated with MLT plus Ang1-7. These results show the possibility to prolong the survival time in untreatable advanced cancer patients by the simple administration of some endogenous anticancer molecules of the human body.

Key words: Angiotensin 1-7, Complementary medicine, Melatonin, Palliative therapy, Pineal gland.

INTRODUCTION

Despite the great advances in cancer therapies, including chemotherapy, anti-angiogenic treatments, targeted therapy, and immunotherapy, the advanced neoplasms yet remain untreatable diseases. Then, after the failure of the standard antitumor therapies, cancer patients are generally considered as suitable for the only best supportive care. Several complementary therapies have been suggested for patients for whom no other conventional

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anticancer therapy may be available, whose aim, however, is generally limited to the improvement of the quality of life and to the treatment of cancer-related symptoms, including pain, anorexia, cachexia, and depression, rather than to influence the clinical course of the neoplastic disease and to prolong the survival time (1). On the other hand, the recent advances in the neuroimmunology have demonstrated that the human body may produced mor than ten anticancer immunostimulatory molecules completely avoided of any toxicity, which are responsible for the natura biological resistance against cancer onset and progression. Therefore, at least from a theoretical point of view, the best complementary Medicine of cancer could consist of the employment of the same endogenous human anticancer immunomodulating molecules (2,3). Unfortunately and paradoxically, almost all complementary medicines seem to prefer the use of natural anticancer agents from plants rather than from human body itself (1-3), which also may produce anticancer molecules. In more detail, according to the results available up to now, the main anticancer endogenous molecules are represented by the pineal hormone melatonin (MLT) (4-6) and angiotensin 1-7 (Ang 1-7) (7-9), which is produced by the enzymatic activity of ACE2 (10). Both MLT and Ang 1-7 have appeared to play an anticancer action through multiple mechanisms, including a direct cytostatic cytotoxic activity, an anti-angiogenic action (4-9), and a stimulation of the anticancer immunity, mainly the IL-2-dependent cytotoxicity (11). Moreover, both MLT (12) and Ang 1-7 (13) may inhibit the secretion of IL-17, which has been proven to play an important pro-tumoral role by directly stimulating cancer cell proliferation (14). Within the endogenous anticancer molecules, the cannabinoids agonists, such as the arachidonyl-ethanol-amide (AEA), the so-called anandamide, and 2-arachidonyl-glycerol (2-AG), have also appeared to play an anticancer activity, mainly due to cytotoxic and anti-angiogenic effects (15). At present, the only data on the employment of natural anticancer agents in the treatment of patients for whom no other standard antitumor therapy may be available regard the only pineal hormone MLT. In more detail, high-dose MLT has been proven to prolong the 5-yearsurvival time in patients with untreatable locally advanced or metastatic solid neoplasms (16). Moreover, MLT anticancer action has appeared to be amplified by a concomitant administration of low-dose Ang 1-7 in terms of objective tumour regression (17), while the impact on the survival has yet to be established. On these bases, a randomized study was planned with high-dose MLT alone or high-dose MLT plus low-dose Ang 1-7 in advanced solid tumor patients eligible for the only palliative therapy.

PATIENTS AND METHODS

The study included 60 consecutive patients, who were suffering from untreatable locally advanced or metastatic solid tumours. Eligibility criteria were, as follows: histologically proven solid neoplasms, locally advanced or metastatic disease, measurable lesions, no availability of standard antitumor therapies because of lack of response to previous treatments, including chemotherapy, targeted therapies, and immunotherapy, no double tumour, and life expectancy lower than one year, or less. After the approval of the Ethical Committee, the clinical protocol was explained to each patient, and written consent was obtained. Then, patients were randomized to receive the best supportive care alone, high-dose MLT alone, or high-dose MLT plus low-dose Ang 1-7. Both MLT and Ang 1-7 were given orally. Moreover, Ang 1-7 was administered in gastro-protected capsules, because of its peptide nature to opposite the gastric degradation. MLT was given at 100 mg/day during the dark period of the day, generally 30 minutes prior to sleep, according to its physiological light/dark circadian rhythm (4-6), while Ang 1-7 was administered at 1 mg/day in the morning, being the period of the maximal ACE-ACE2 axis activity (7-9). Moreover, according to previous studies (16), patients under therapy with MLT alone or MLT plus Ang 1-7 received some other complementary natural agent, including Aloe, Myrrh, Magnolia, cannabidiol, 5-methoxytryptamine, and anti-proliferative mushrooms (1-3). The treatment was continued every day without interruption until disease progression or eventual toxicity. The clinical response was evaluated according to WHO criteria, by repeating the radiological examinations, including CT scan, NMR and PET, at 3-month intervals. Moreover, the immunobiological response was assessed by measuring lymphocyte-to-monocyte ratio (LMR), which has appeared to be the simplest and less expensive biomarker to predict the prognosis of advanced cancer patients(18). Normal values of LMR observed in our laboratory(95% confidence limits) was more than 2.1. Data were statistically analysed by the chi-square test and the Student's t test, as appropriate. Moreover, the survival curves were made according to the Kaplan-Meyer method, and statistically evaluated by the log-rank test.

RESULTS

The clinical characteristics of patients are reported in ***Table 1.*** As shown, the three group of patients were well balanced for the main prognostic factors, including tumor his to types, metastasis sites, disease extension, and age. No tumor regression occurred in patients treated with the only palliative therapy. A stable disease (SD) was seen in 3/20 (15%) patients, whereas the other 17 (85%) rapidly progressed within the first three months of observation. A partial response (PR) was achieved in 1/19 (5%) patients treated with MLT alone, and in 2/21 (9%) patients concomitantly treated with Ang 1-7. Moreover, a SDwas obtained in 11/19 (64%) patients treated

with MLT alone, and in 14/21 (67%) patients concomitantly treated with Ang 1-7. Then, the percentage of disease control (RP + SD)achieved in patients concomitantly treated with Ang 1-7 was higher than that found in those treated with MLT alone (16/21 (76%)vs 12/19 (63%)), without, however, statistically significant differences. The percent of 1-year survival curves are illustrated in **Figure 1**. As shown, the percent of 1-year survival observed in patients treated with the only palliative therapy, MLT alone or MLT plus Ang 1-7 were respectively 1/20 (5%), 9/19 (47%), and 17/21 (81%). Then, the percentage of 1-year survival achieved in both groups of patients treated with MLT or MLT plus Ang 1-7 was significantly higher with respect to that found in patients treated with the only best supportive care (P<0.001). Moreover, the percent of 1-year survival obtained inpatients concomitantly treated with Ang 1-7 was significantly higher with respect to that found in those treated with MLT alone (P< 0.05). No MLT- and Ang 1-7-related toxicity was observed. On the contrary, both patients treated with MLT alone or MLT plus Ang 1-7 referred a mood improvement and a progressive relief of asthenia, which was particularly evident in those concomitantly treated with Ang 1-7.

Table 1. Clinical characteristics of 60 untreatable advanced cancer patients treated by high-dose melatonin (MLT) alone, high-dose MLT plus angiotensin 1-7 (Ang 1-7), or the supportive care alone as controls.

CHARACTERISTICS	MLT + Ang 1-7	MLT	CONTROLS
n	21	19	20
M/F	9/12	10/9	9/11
Median age (years)	64 (5-82)	62 (15-79)	61 (21-81)
HISTOTYPES			
-Glioblastoma	5	3	4
-Colorectal cancer	5	4	5
-Pancreatic cancer	1	2	2
-Gastric cancer	1	1	2
-Biliary tract cancer	1	2	1
-Lung adenocarcinoma	1	1	2
-Breast cancer	2	2	1
-Gynaecologic tumours	1	1	1
-Renal cancer	1	0	0
-Sarcoma	2	1	1
-Melanoma	1	2	1
METASTATIC DISEASE	16/21 (76%)	16/19 (84%)	16/20 (80%)
-Nodes	1	2	1
-Bone	1	1	2
-Lung	3	3	4
-Liver	5	5	4
-Peritoneum	3	2	3
-Brain	3	3	2

DISCUSSION

According to previous clinical investigations (16), the results of the present study confirm that high-dose MLT may prolong the survival time in advanced solid tumor patients, for whom no other conventional anticancer therapy was available, and life expectancy less than one year. Moreover, as previously reported(17), the concomitant administration of low-dose Ang 1-7 may enhance the antitumor efficacy of high-dose MLT in terms of tumor regressions and stabilization of disease. In addition, the results of this study show that the neuroimmune antitumor regimen with high-dose MLT plus low-dose Ang 1-7 may not only control tumour growth, but also prolong the 1-year survival time in untreatable advanced cancer patients because of the lack of response to the previous standard anticancer therapies, then with life expectancy less than one year or less. The better results obtained in patients concomitantly treated with Ang 1-7 could depend on the direct anticancer activity of Ang 1-7 itself (7-9), as well as on the possible promoting effect of MLT on the activation of ACE2-Ang1-7/ Mas receptor axis (18). Obviously, further studies in a greater number of patients will be required to establish which tumor histotype may be particularly responsive to the treatment. In any case, the results of this study are not

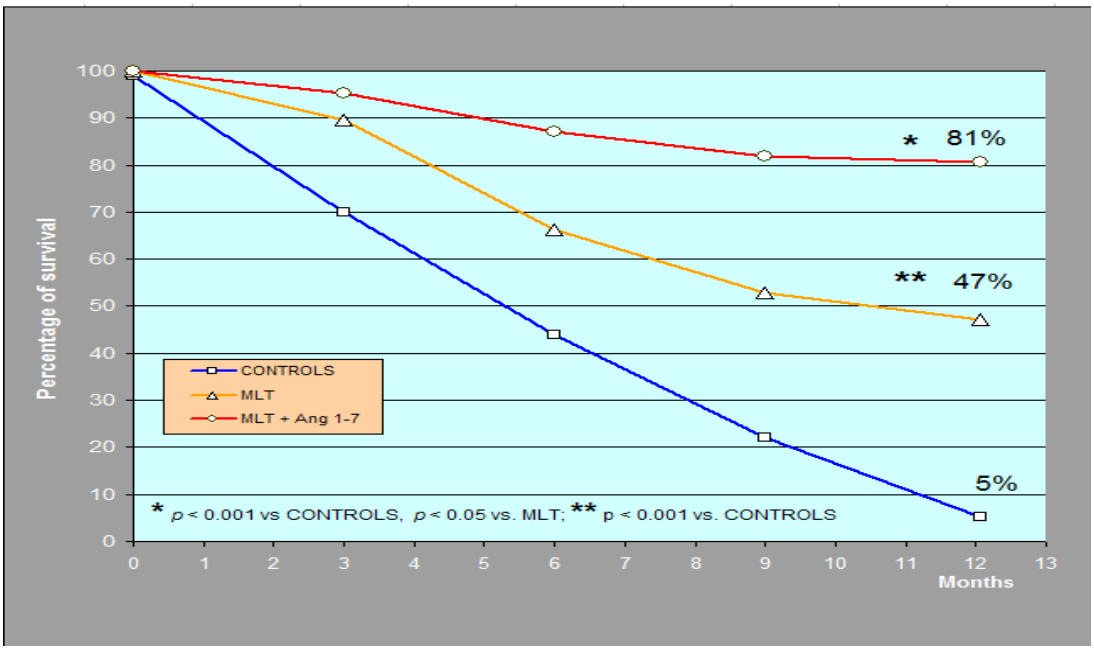

Figure 1. 1-year survival in advanced cancer patients, who received melatonin (MLT) alone, MLT plus angiotensin 1-7 (Ang 1-7), or the only supportive care.

surprising, since both MLT and Ang 1-7 have been proven to be provided by important anticancer activities by inhibiting both cancer cell proliferation and angiogenesis (4-9), and stimulating the anticancer immunity, as shown by the improvement in LMR ratio in responder patients, whose increase has been shown to predict a more favourable clinical course and a prolonged survival in advanced cancer patients (19). Therefore, in addition to the recent immunotherapies with immune checkpoint inhibitors (20), the results of this study would suggest the possibility to improve the anticancer immune reaction through the same physiological mechanisms involved in inducing the natural anticancer immunobiological resistance. In fact, both MLT (11,12) and Ang 1-7 (13) have appeared to activate the anticancer immunity. MLT may modulate the immune system in an antitumor way by stimulating Th1 cell-dependent secretion of IL-2 (11), the main anticancer cytokine in humans (21), and IL-12 production from mature dendritic cells (11), by inhibiting the release of the pro-tumoral cytokine IL-17 (12), and by enhancing IL-2-induced lymphocyte increase (22). On the other side, the immunomodulating properties of Ang 1-7 are less investigated, but they include at least an inhibition ofIL-17 secretion (13), and an inhibition of macrophage-mediated inflammatory and immunosuppressive activity (23), which has been proven to be responsible for cancer progression (24). Then, the major target for MLT anticancer immune action would consist of lymphocyte system itself, while that of Ang 1-7 could be fundamentally represent by the endothelial system (7-9), whose characteristics may influence its permeability to cancer cell migration, and to the angiogenic processes. In addition, it must be remarked that pineal gland and ACE2-Ang 1-7 axis are physiologically connected by reciprocal links, and particularly it has been shown that MLT may inhibit ACE expression and promoting that of ACE2, with a consequent enhanced Ang 1-7 production (18). Obviously, the biological activity of Ang 1-7 depends on both its production and the expression of its Mas receptor. If Ang 1-7 secretion is mainly stimulated by the pineal hormone MLT, the expression of both ACE2 and Ang 1-7 receptor expression could by stimulated by the endogenous cannabinoid anandamide, as well as by other cannabinoid CB1-CB2 agonist (25). Unfortunately, at present only few preliminary data are available about the relationships occurring between the endocannabinoid system and ACE2-Ang 1-7-Mas receptor axis (25). However, it is already known that anandamide exert direct antitumor antiproliferative anti-angiogenic effects (15), and important immunomodulatory effects, namely the inhibition of IL-17 secretion (26). Therefore, the concomitant administration of anandamide could furtherly enhance the antitumor properties of the neuroendocrine regimen with MLT plus Ang 1-7 by restoring the activity of the three major antitumor anti-inflammatory biological systems of the human body, consisting of the pineal gland, then endocannabinoid system and ACE2-Ang 1-7-Mas receptor axis. Therefore, the evaluation of the efficacy of a neuroendocrine protocol with MLT, Ang 1-7 and anandamide will the aim of future clinical studies in advanced cancer patients eligible for the only best supportive care.

CONCLUSION

This study shows that the antitumor regimen with MLT plus Ang 1-7 may play a therapeutic efficacy with respect to that with MLT alone, also in patients who failed to respond to the standard anticancer therapies, and who are generally considered as suitable for the only palliative therapy.

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