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Research Article

A Phase-2 Study On The Efficacy Of Low-Dose Anandamide Plus A Neuroendocrine Regimen With High-Dose Melatonin And Low-Dose Angiotensin 1-7 In Patients Affected By Untreatable Glioblastoma

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Abstract

Glioblastoma (GBM) still represents the most aggressive human neoplasm. The recent advances in the area of psychoneuroendocrinoimmunology (PNEI) have demonstrated that GBM is under a neuroendocrine regulation, since it has been shown to be stimulated by mu-opioid agonists and to be inhibited by the pineal hormones melatonin (MLT) and 5-methoxytryptamine (5-MTT), the cannabinoid agents, particularly cannabigerol (CBG), and angiotensin 1-7 (Ang 1-7). Moreover, preliminary clinical studies have suggested the potential efficacy of a neuroendocrine regimen consisting of MLT, 5-MTT, CBG, and Ang 1-7 in GBM patients progressed under the standard therapy with radiotherapy plus temozolomide. On these bases, a preliminary study was planned to evaluate the efficacy of the administration of the endogenous CB1-agonist anandamide in GBM patients, who progressed under both the conventional therapy and the neuroendocrine regimen with pineal hormones, Ang 1-7 and CBG. All drugs were given orally, MLT at 100 mg/day in the night, 5-MTT at 20 mg/day in the early afternoon, Ang 1-7 at 0.5 mg twice/day, CBG at 20 mg twice/day, and AEA at 0.5 mg/day in the morning. No complete response was observed. A partial response (PR) was achieved in one patient. Moreover, a stable disease (SD) occurred in 7 patients. Then, the percentage of disease control (PR + SD) was 8/14 (57%). Finally, a survival longer than 1 year was achieved in 5/14 (36%). No toxicity was observed. On the contrary, patients improved their mood and status of consciousness, and 5 of them referred a status of bliss. The results of this preliminary study would suggest a potential therapeutic role of AEA in GMB, also in patient with very advanced disease already under therapy with exogenous cannabinoids.

Keywords: Anandamide, Angiotensin 1-7, Cannabigerol, Glioblastoma, Pineal hormones.

Introduction

Glioblastoma (GBM) still remains un untreatable disease, and the survival is generally less than one year or 18 months (1). The lack of an effective therapy of GBM would be due at least in part to the only partial knowledge of the biological mechanisms responsible for the stimulation, or the inhibition of GBM onset and development. The recent advances in the knowledge of the pineal gland and most in general in the investigation of the psycho-neuro-endocrine-immunology (PNEI) have demonstrated the existence of three major biological system provided by bio-regenerative antitumor, anti-inflammatory, anti-thrombotic, and anti-fibrotic activities, consisting of the pineal gland (2) through the nocturnal release of its most known indole

hormone melatonin (MLT), the other less investigated indole 5-methoxytryptamine (5-MTT) (3), and beta-carbolines (4), the endocannabinoid system (5), and the ACE2-angiotensin 1-7 (Ang 1-7) axis (6). Despite the great number of experimental studies confirming their efficacy, very few clinical studies are available up to now about the potential efficacy of the pineal hormones, the cannabinoid agents, and Ang 1-7 in the treatment of cancer and most in general of the human systemic diseases. However, preliminary clinical studies have shown the potential efficacy of a neuroendocrine regimen with the pineal hormones in association with Ang 1-7, and exogenous cannabinoid agents, such as cannabidiol (CBD) and cannabigerol (CBG), in the treatment of patients affected by advanced untreatable tumors, autoimmune, and neurodegenerative diseases (7,8). From a pharmacological point of view, it is known that the cannabinoid agents may be subdivided into two major classes, consisting of direct CB1-CB2 agonists, and inhibitors of fatty acid amide hydrolase (FHHA), the enzyme responsible for cannabinoid degradation (5). Then, the inhibition of FAAH activity allows an increase in the endogenous cannabinoid content. The psychotropic psychedelic effect of cannabinoids is mediated by the CB1 receptor, which is expressed by most cells, while CB2 receptor is only expressed by few types of cells, including immune and osteoblastic cells (5). The main endogenous CB1-CB2 agents are represented by arachidonyl-ethanol-amide (AEA) (5,9), also termed anandamide because of its effects of bliss, and 2-arachidonyl-glycerol (2-AG) (5,10), whose psychobiological effects have been less investigated. The pineal hormones MLT and 5-MTT, the endocannabinoids AEA and 2-AG, and Ang 1-7 have been proven to exert an anticancer activity without any evident toxicity through several mechanisms, including a direct antiproliferative cytotoxic effect, an anti-angiogenic action, and a stimulation of the anticancer immunity by promoting IL-2 secretion from TH1 lymphocytes (11), and by inhibiting IL-17 secretion from TH17 lymphocytes (12) and IL-6 and TNF-alpha from macrophages (13). Moreover, pineal gland, endocannabinoid system, and ACE2-Ang 1-7 axis have appeared to be connected by reciprocal stimulatory actions. In more detail, the cannabinoid agents have been proven to stimulate the pineal release of MLT (14), which in turn inhibits ACE expression, and stimulates that of ACE2 (15), with a consequent enhanced production of Ang 1-7, which finally promotes cannabinoid receptor expression (16). The stimulatory action of MLT on ACE2 expression allows the possibility to reduce the dose of Ang 1-7 required to exert clinical effects (8). Moreover, at present the few clinical studies with MLT and Ang 1-7 in the treatment of human systemic diseases have employed CBD, a non-psychotic and a non-CB1 agonist cannabinoid agent, because of its anti-inflammatory, anxiolytic, and antalgic effects (5,7,8). On the contrary, at present there is no clinical study with a CB1 agonist, such as the endogenous AEA and 2-AG, or the exogenous tetrahydrocannabinol (THC), in association with pineal hormones and Ang 1-7 in the treatment of advanced neoplasms and other systemic diseases. Being both AEA and THC CB1 agonist agents, the effects of AEA has been generally considered to be similar to those of THC, but this equivalence of effects is not absolute, since THC enhances the perception of pleasure, and amplifies the sexual fancies (5), while the main effect of AEA would be represented by bliss and serenity (17). Finally, as far as the anticancer action, at present no clinical study has demonstrated an eventual superiority of CB1 agonists with respect to FAAH inhibitors in the control of tumor growth (5). As far as GBM is concerned, at present it is known that GBM growth is stimulated by mu-opioid agonists, such as beta-endorphin and morphine (18), since the expression of mu-opioid receptor has been found to be associated with a poor prognosis and a lower survival (19). On the contrary, GBM growth is inhibited by both the pineal hormone MLT (2) and cannabinoid agents (5,20). On these bases, a phase-2 preliminary study has been performed by a neuroendocrine regimen with the pineal hormones MLT and 5-MTT, CBG, low-dose Ang 1-7, and low-dose AEA in patients affected by GBM, who progressed after the standard radio-chemotherapy, and also under a previous neuroendocrine regimen without AEA, then for whom no other effective therapy was available.

Patients And Methods

The phase-2 study included 14 consecutive GBM patients (M/F: 8/6; median age 64 years, range 42-78 years), who progressed under either the standard radio-chemotherapy with temozolomide, or a same previous neuroendocrine regimen without AEA. Eligibility criteria were, as follows: histologically proven GBM, measurable lesions, no availability of other conventional therapies because of progression under either the standard radio-chemotherapy with temozolomide, or a neuroendocrine therapy with pineal hormones, Ang 1-7, and CBG, then eligible for the only best supportive care, and life expectancy less than 6 months. We preferred CBG than CBD because of its apparent greater efficacy in the treatment of GBM (20). After the approval of the Ethical Committee, the clinical protocol was explained to each patient, and written consent was obtained.

All drugs were administered orally. Ang 1-7 was given in gastro-protected capsules by cyclodextrin, and AEA in oil at 0.1 mg for drop. MLT was given at 100 mg/day in the night, generally 30 minutes prior to sleep. 5-MTT was administered at a dose of 20 mg/day in the early afternoon. CBG was administered at 20 mg twice/day. Ang 1-7 was given at 0.5 mg twice/day in the morning and in the evening. Finally, AEA was administered at 0.5 mg in the morning, by starting from a dose of 0.1 mg, and by increasing the dose of 0.1 mg every day, until reaching the planned dose of 0.5 mg/day. AEA was given at low doses since it has appeared to be biologically active also at very low dosages (21), as well as because of the stimulatory action of MLT on the endogenous production of AEA (22). Patients were considered to be evaluable when they were treated for at least 3 consecutive months. The clinical response was evaluated according to WHO criteria. Moreover, the immune status of patients was assessed by detecting lymphocyte-to-monocyte ratio (LMR) prior to the onset of the study and at 15-day intervals, since its progressive decline has been proven to predict tumor progression and a worse prognosis in advanced cancer patients (23).

Data were reported as mean +/- SE, and statistically evaluated by the chi-square test, the Student's t test, and the

analysis of variance, as appropriate.

Results

As reported in Table 1, the clinical response obtained in GBM patients consisted of a partial response (PR) in 1/14 (7%) patients, and a stable disease (SD) in other 7/14 (50%) patients. Then, a disease control (DC) (PR + SD) was achieved in 8/14 (57%) patients, whereas the remaining 6/14 (43%) patients had a progressive disease (PD). The median duration of DC was 8 months (range 5-14+ months). Moreover, a survival longer than one year was achieved in 5/14 (36%) patients. Finally, the percentage of 1-year survival obtained in patients with DC was significantly higher than that observed in patients with PD (6/8 (75%) vs 0/6, P<0.01). In addition, the percentages of both DC and 1-year survival observed in male patients were significantly higher than those found in female patients (P<0.05). No biological toxicity occurred. On the contrary, most patients referred an improvement in mood and quality of sleep in association with a decrease in anxiety and asthenia. Moreover, 4/14 (29%) patients referred an evident bliss, never experienced in their past life, in association with a clear improvement in their cognitive functions.

As far as the immune response is concerned, LMR mean levels enhanced in patients with DC, whereas it decreased or remained unchanged in patients, who had a PD, and LMR values observed after at least one month of therapy were significantly higher than those found in patients with PD (2.7 +/- 0.3 vs 1.8 +/- 0.1, P<0.05.

Discussion

As previously observed in experimental conditions (7), this preliminary phase-2 clinical study seems to suggest that the administration of the endogenous cannabinoid AEA may counteract the growth of GBM also in patients who did respond neither to the standard therapy, nor to a neuroendocrine regimen with pineal hormones and Ang 1-7 plus exogenous cannabinoids, with more evident effects in males than in females. AEA could also amplify the neuroprotective effect of MLT (22), by counteracting GBM mass-associated neuroinflammation, which could promote the growth of GBM itself. Therefore, AEA could constitute a further hope also for patients, who progressed under both standard treatment and neuroimmune approach. Moreover, the results of this study show that the control of tumor growth is associated with an improvement in the immune status, as confirmed by the increase in LMR values, which has been found to predict a longer survival (23). Then, this preliminary study would justify further clinical researches with AEA in the treatment of brain tumor, at least to improve their mood and consciousness status. Obviously, further randomized studies will be required to confirm the clinical usefulness of AEA in the treatment of human tumors, particularly GBM. Moreover, more adequate immune investigations, including the measurement of changes in lymphocyte subpopulation and in blood levels of the most important protumor and antitumor cytokines, will be necessary to better establish which relation may exist between changes in immune functions and control of cancer growth. Then, the clinical use of both endogenous and exogenous cannabinoids from Cannabis may disclose a new era in the treatment of human tumors, and in particular of brain tumors, which could be the consequence of an unbalance between opioid and cannabinoid systems at brain level (5,20).

Table 1: Clinical response (WHO criteria) in 14 glioblastoma patients eligible for the only palliative therapy treated by the pineal hormone, melatonin and 5-methoxytryptamine, angiotensin 1-7, cannabigerol, and anandamide.

PATIENTS	n	CLINICAL RESPONSE					
		CR	PR	SD	DC	PD	1-YEAR SURVIVAL
OVERALL PATIENTS	14	0	1 (7%)	7 (50%)	8 (57%)	6 (43%)	5 (36%)
MALES	8	0	0	6 (75%)	6 (75%)**	2 (25%)	4 (50%)**
FEMALES	6	0	1 (17%)	1 (17%)	2 (33%)	4 (67%)	1 (17%)

***CR: complete response: PR: partial response; SD: stable disease; DC: disease control; PD: progressive disease.**
****P<0.05 vs females**

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