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Research article

A PsychoNeuroEndocrineImmune (PNEI) Approach to Enhance the Efficacy of Radiochemotherapy in Glioblastoma

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Abstract

GBM would represent perhaps the only tumor, whose prognosis had achieved no evident benefits in terms of survival from the main oncological therapies, including chemotherapy, immunotherapy and anti-angiogenic treatments. According to the recent advances in the Psychoneuroendocrinology, an improvement in GBM therapy could arise from the knowledge of the psychoneuroendocrine mechanisms responsible for GBM cancer cell growth, and, at present, it has been proven that GBM cells may express opioid receptors, whose activation stimulate cancer proliferation, whereas melatonin (MLT) and other pineal indole hormones, namely the 5-methoxytryptamine (5-MTT), may suppress GBM growth. In addition, several plants, such as Aloe, Myrrh, Boswellia, Magnolia and Cannabis Indica, have appeared to exert an anticancer activity on several tumor histotypes, including GBM. On these bases, a study was planned by associating a neuroendocrine and phytotherapeutic combination to the standard therapy of GBM with radiotherapy (RT) plus chemiotherapy of temozolomide (TMZ). The study included 30 consecutive patients with histologically proven GBM after radical or palliative surgery. The neuroendocrine regimen consisted of an oral administration of MLT at 100 mg/day in the dark period plus 5-MTT at a dose of 5 mg/day in the light period of the day plus the opioid antagonist naltrexone (NTX) at escalating doses until a maximal dosage of 50 mg/day in the morning. The phytotherapeutic regimen included Aloe, Myrrh, Magnolia and Boswellia. Finally, patients were randomized to received also Cannabis infusion. A disease control, including partial response and stable disease, was achieved in 16/30 (53%) patients, and it was associated with a survival longer than 1 year in 17/30 (57%) patients. At the end, the 3-year survival achieved in patients concomitantly treated by Cannabis was significantly higher that that found in patients, who received no Cannabis therapy. This preliminary study would suggest that a neurorendocrine approach, carried out to biologically counteract GBM growth, in association with the standard therapy with RT plus TMZ may increase the overall survival of GBM patients.

Keywords: Glioblastoma; Melatonin; Naltrexone; Opioid system Pineal gland

Introduction

Brain glioblastoma (GBM) still remains the most untreatable neoplastic disease. Several factors have been taken into consideration to identify possible subtypes of GBM with different prognostic behaviour, but, at present, the main prognostic factors would be represented by age, performance status (PS) and methyl-guanine DNA-methyltransferase (MGMT). The prognosis is worse in aged patients and in those with low PS. In patients 60 year older the overall survival time is generally less than 6-9 months [1,2]. In contrast, patients positive for MGMT expression would have a longer survival and a better response to chemotherapy [3]. Almost all clinical therapeutic studies, performed up to now, have been carried out with the only radiotherapy (RT) and chemotherapy (CT). Only the temozolomide (TMZ) has been substantially used as potentially active chemotherapeutic agent, without taking into consideration the possible existence of endogenous growth factor stimulating GBM cancer cell growth, as well as estrogens for breast cancer and androgens for prostate cancer, and, on the other hand, pos-

sible endogenous inhibitory factors on GBM cancer cell proliferation. In fact, it is known since many years that GBM cells may express mu-opioid receptors and that mu-opioid agents may stimulate GBM cancer cell growth [4].

Therefore, the evidence of tumor mu-opioid receptors expression would be associated with a poor prognosis, because of the stimulatory action of mu-opioid agonists, such as beta-endorphin, on cancer growth. On the contrary, the pineal indole hormones [5] and the cannabinoid agonists from Cannabis Indica [6] have been proven to inhibit GBM cell proliferation. Melatonin (MLT) represents the most investigated pineal hormone provided by a well documented anticancer activity on several tumor histotypes, including GBM [5], but at least another pineal indole hormone, the 5-methoxytryptamine (5-MTT), has appeared to exert in vitro an anticancer action superior to that of MLT itself [7]. In addition, cancer progression has been proven to be associated with a progressive decline in MLT secretion, mainly during the night [8], and most in general with a diminished pineal endocrine function [9]. MLT exerts its effects by acting on specific MLT receptors MT 1 and MT 2 ([10], and it has been demonstrated that tumor expression of MLT receptors are associated with a better prognosis in cancer patients [11]. Pineal deficiency may be corrected by an exogenous administration of the main pineal indole hormones, whereas the stimulatory activity of brain opioid system may be counteracted by the administration of the long-acting opioid antagonist naltrexone (NTX) [12].

On the basis of these data and according to a neuroendocrine strategy, it seems to be justified the employment of pineal hormones and opioid antagonists in the treatment of GBM in association with the standard radiochemotherapeutic regimen or after progression on RT plus CT with TMZ. This preliminary phase 2 study was carried out to evaluate the impact of a neuroendocrine schedule with pineal hormones and opioid antagonists in association with the standard therapy by RT plus CT in the treatment of GBM.

Materials and Methods

The study included 30 consecutive GBM patients, who underwent the standard treatment with RT plus CT with TMZ in association with a neuroendocrine regimen consisting of the oncostatic pineal hormones MLT and 5-MTTplus the mu-opioid antagonist NTX. Eligibility criteria were as follows: histologically proven GBM, measurable lesions, macroscopically radical or palliative surgery, and life expectancy less than 1 year. The experimental protocol was explained to patients, and their consent was obtained. The clinical characteristics of patients are reported in Table 1. The standard treatment consisted of RT 60 Gy in 2-Gy 30 fractions plus TMZ at 75 mg/m^2/day orally during RT, followed by 6 cycles of TMZ at 200 mg/m^2/day for 5 consecutive days every 28 days. The pineal endocrine therapy consisted of an oral administration of MLT at 100 mg/day during the dark phase of the day plus 5-MTT at a dose of 10 mg/day during the light phase of the day, corresponding to the time of their circadian secretion. Moreover, in case of progression, because of the evidence of a dose-dependency in its antitumor activity [13], MLT dose was increased of 100 mg/day every time, until a maximal dosage of 500 mg/day. NTX was given orally at a daily dose of 50 mg, starting with a dose of 20 mg/day in the morning by slowly increasing the dose of 10 mg every month in an attempt to reduce liver toxicity of NTX [12]. The supportive care with natural agents consisted of the oral administration of antitumor plants, including a mixture of Aloe arborescens [14] plus Myrrh [15] (60/ 40% ratio) at a dose of 10 ml thrice/day, Magnolia cortex at 500 mg twice/day [16], and Boswellia [17], also provided by an anti-oedema activity, at 1000 mg twice/day. At the end, according to their free adhesion and compliance, patients were randomized to receive also Cannabis flos (19% tetra-hydro-cannabinol) as an infusion of Cannabis 0.5 mg/ liter of water, by drinking it at 100 ml three times/day. The clinical response was evaluated by WHO criteria. Data were statistically analyzed by the chi-square test, the Student's test and the log-rank test, as appropriate.

M / F	20 / 10
Median age (years)	65 (range 21-75)
Median PS (ECOG)	1 (range 0-3)
Tumor sites	
- Frontal cortex	13
- Temporal cortex	7
- Temporo- parietal cortex	5
- Occipital cortex	2
- Corpus callosum	3

Table 1. Clinical characteristics of 30 GBM patients.

Results

The clinical response (WHO) is shown in Table 2. A macroscopically radical surgery was obtained in no patient. No complete response (CR) was achieved after RT plus CT. A partial response (PR) was obtained in 3/13 (23%) patients treated also by Cannabis and in none of the 17 patients, who received no Cannabis infusion. A stable disease (SD) occurred in 6/17 patients treated without Cannabis and in 7/13 patients under Cannabis treatment. Therefore, the percentage of disease control (DC) (PR + SD) obtained in patients concomitantly treated with Cannabis was significantly higher with respect to that found in patients, who did not receive Cannabis infusion (10/13 (77%) vs 6/17 (35%), $P < 0.05$). The percent of 3-year survival is illustrated in Figure 1. A survival longer than 1 year and than 3 years was achieved in 17/30 (57%) and in

5/30 (17%) patients, respectively. Moreover, the percentage of 3-year survival achieved in patients concomitantly treated by Cannabis was significantly longer than that found in patients who did not receive Cannabis infusion (4/13 (31%) vs 1/17 (6%), P < 0.05).

CLINICAL RESPONSE +						
PATIENTS	n	CR	PR	SD	DC	PD
ALL PATIENTS	30	0	3	13	16	14
CANNABIS	13	0	3	7	10 *	3
NO CANNABIS	17	0	0	6	6	11

+ CR: complete response; PR: partial response; SD:stable disease; DC (CR +PR+SD): disease control; PD: progressive disease.

* P <0.05 vs no Cannabis

Table 2. Clinical response (WHO) to radio-chemotherapy plus neuroendocrin approach plus or without Cannabis infusion in GBM patients.

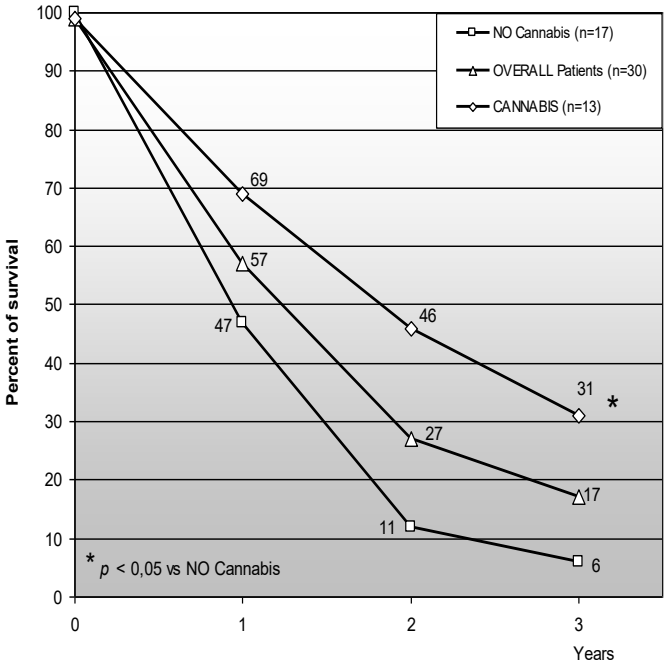

Figure 1. Survival curves in GBM patients on neuroendocrine therapy with or without Cannabis infusion.

The neuroendocrine treatment was well tolerated in all patients. No biological toxicity occurred, and the only side-effect was sleepiness or paradoxical excitation for few days in 5/30 (17%) under high-dose MLT administration. On the contrary, most patients referred an improvement in their mood and a mild relief of asthenia. Finally, no cancer progression-related cachexia occurred.

Discussion

With respect to the expected survival time and by considering that most GBM patients included in the clinical investigation were 60-year older, therefore with an expected survival time generally less than 9 months [1, 2], the results of this preliminary study would show that the survival of GBM patients may be improved by associating to the standard radio-chemotherapy schedule the administration of an oncostatic neuroendocrine regimen, consisting of antitumor pineal hormones plus opioid antagonists in association with plants with well documented anticancer antiproliferative immunomodulating properties. Obviously, randomized clinical studies will be required to confirm the therapeutic efficacy of a concomitant neuroendocrine phytotherapeutic combination in association with the standard radio-chemotherapy in the treatment of GBM. However, the survival achieved by this combination has been clearly superior to that described by previous clinical studies of GBM patients treated with MLT alone after progression under RT [18]. Moreover, this study would suggest that the further association of cannabinoids may prolong the survival time with respect to GBM patients, who did not received Cannabis infusion. This evidence is not surprising, since cannabinoid have been proven to exert direct antiproliferative and anti-angiogenic effects on several tumor histotypes, including brain GBM [6]. The evaluation of mu-opioid [4] and MLT receptor expression [10, 11] on GBM cells could identify possible subgroups of tumors with different prognostic profiles, and in more detail cancer expression of MT receptors could predict a better prognosis [11], whereas that of mu-opioid receptors would be associated with a poor prognosis, because of the stimulatory role of opioids on GBM cancer cell proliferation [4]).Therefore, the identification of MLT and opioid receptor expression on GBM cells could allow to identify possible subgroups of patients, who could obtain more benefits from a neuroendocrine approach with pineal hormones and opioid antagonists.

In conclusion, this study would simply represent only the first suggestion to further explore the therapeutic efficacy of a neuroendocrine strategy in the treatment of GBM, consisting of the administration of the same endogenous hormones provided by an anticancer activity on GBM cell growth, namely the pineal hormones, in association with opioid antagonists to inhibit the brain opioid system, which would play a stimulatory role on GBM development [4].

Further therapeutic results could be achieved by associating the neuroendocrine-approach in GBM therapy to the more recent immunotherapeutic techniques with anti-immune check-point monoclonal antibodies, mainly those against CTLA-4 and PD-1 [19-21].

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References

1. Brandles AA. State of the art treatment for high grade brain tumors. Semin Oncol. 2003, 30 (6 Suppl 19): 4-9.

2. Hentschel SJ, Sawaya R. Optimizing outcomes with maximal surgical resection of malignant gliomas. Cancer Control. 2003, 10(2): 109-114.

3. Gerson SL. MGMT: its role in cancer aetiology and cancer therapeutics. Nat Rev Cancer. 2004, 4(4): 296-307.

4. Westphal M, Li CH. Beta-endorphin: characterization of binding sites specific for the human hormone in human glioblastoma SF 126 cells. Proc Natl Acad Sci USA. 1984, 81: 2921-2923.

5. Reiter RJ. Mechanisms of cancer inhibition by melatonin. J Pineal Res. 2004, 37(3): 213-214.

6. Grotenhermen F. Pharmacology of cannabinoids. Neuroendocrinol Lett. 2004, 25(1-2): 14-23.

7. Sze SF, Ng TB, Liu WK. Antiproliferative effect of pineal indoles on cultured tumor cell lines. J Pineal Res.1993, 14(1): 27-33.

8. Brzezinski A. Melatonin in humans. N Engl J Med.1997, 336(3): 186-195.

9. Maestroni GJM. The immunoneuroendocrine role of melatonin. J Pineal Res.1993, 14(1): 1-10.

10. Danielczyk K, Dzjegiel P. MT 1 melatonin receptors and their role in the oncostatic action of melatonin. Postepy Hig Med Dosw. 2009, 63: 425-434.

11. Nemeth C, Humpeler S, Kallay E, Mesteri I, Svoboda M et al. Decreased expression of the melatonin receptor 1 in human colorectal carcinomas. J Biol Regul Homeost Agents. 2011, 25(4): 531-542.

12. Krabtee BL. Review of naltrexone, a long-acting opioid antagonist. Clin Pharm. 1984, 3(3): 237-281.

13. Lissoni P, Porro G, Messina G, Porta E, Rovelli F et al. Morphine, melatonin, marijuana, magnolia and myrrh as the "five M" schedule in the treatment of cancer pain and the possible dose-dependency of the antitumor and analgesic effects of the pineal hormone melatonin. Anticancer Res. 2014, 34(10): 6033-6034.

14. Guo J, Xiao B, Liu Q, Gong Z, Le Y. Suppression of c-myc expression associated with anti-proliferation of aloe-emodin on gastric cancer cells. Cancer Invest. 2008, 26(4): 369-374.

15. Hanus LO, Rezanka T, Dembitsky VM, Moussaief A. Myrrh-Commiphora chemistry. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2005, 149(1): 3-28.

16. Fried LE, Arbiser J. Honokiol, a multifunctional antiangiogenic and antitumor agent. Antioxid Redox Signal. 2009, 11(5):1139-1148.

17. Tucker AO. Frankincense and Myrrh. Econ Bot. 1986, 40(4): 425-433.

18. Lissoni P, Meregalli S, Nosetto L, Barni S, Tancini G et al. Increased survival time in brain glioblastoma by a radioneuroendocrine strategy with radiotherapy plus melatonin compared to radiotherapy alone. Oncology. 1996, 53(1): 43-46.

19. Pardoll DM. The blockade of immune check points in cancer immunotherapy . Nat Rev Cancer. 2012, 12(4): 252-264.

20. Weber J. Immune check points proteins:a new therapeutic paradigm for cancer pre-clinical background: CTLA-4 and PD-1 blockade. Sem Oncol. 2010, 37(5): 430-439.

21. Ascierto PA, Kalos M, Schaer DA, Callahan MK, Wolchok JD. Biomarkers for immunostimulatory monoclonal antibodies in combination strategy for melanoma and other cancer types. Clin Canc Res. 2013, 19(5):1009-1020.