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# A Preliminary Study on the Anticancer Properties of Oxytocin: A Neuroendocrine Regimen with Oxytocin, Antitumor Pineal Indoles, and Cannabidiol in Untreatable Advanced Cancer Patients Progressing on Pineal Indoles and Cannabidiol Alone

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**ABSTRACT**

The recent discovery of several endogenous and exogenous anticancer non-toxic molecules has allowed the possibility to administer potential anticancer curative regimens also in patients, who would be generally considered as eligible for the only palliative therapy. Within the anticancer molecules of the human body, it has been shown that the pineal indole hormones and the endocannabinoid agents may play an anticancer activity against most tumor histotypes through several mechanisms, including cytotoxic, anti-angiogenic and immunostimulatory effect on the anticancer immunity, and to prolong the survival time in advanced cancer patients eligible for the only supportive care. In fact, cancer progression has appeared to be associated with a progressive decline in the functionless of the pineal gland and endocannabinoid system. The endocannabinoid brain activity may be enhanced by the non-psychoactive principle of the cannabis plant, the cannabidiol (CBD), because of its capacity of inhibiting the enzyme involved in cannabinoid degradation, the fatty acid amide hydrolase (FAAH). Moreover, the neurohypophyseal hormone oxytocin (OXY) has recently appeared to play an anticancer activity, namely in breast cancer, including the triple negative breast cancer (TNBC), gynecologic tumors and brain neoplasms, and its production would be abnormally low in advanced cancer patients. On these bases, a study was planned to establish whether the concomitant administration of OXY may again determine a control of cancer progression in patients eligible for the only palliative therapy after their progression on therapy with the only pineal hormones plus CBD. The study was limited to tumor histotypes potentially responsive to OXY, including breast cancer, gynecolgic tumors and brain glioblastoma (GMB). The study included 14 consecutive patients (gynecologic tumors: 7; TNBC: 4; GBM: 3). The pineal indoles melatonin (MLT) and 5-methoxytryptamine

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(5-MTT) were given orally at 100 mg/day in the dark period, and at 10 mg/day in the light period, respectively. CBD was also given orally at 10 mg twice/day. Finally, OXY was given orally at 2 mg twice/day in a gastroprotected form. A stable disease (SD) was achieved in 8/14 (57%) patients (gynecologic tumors: 5; TNBC: 2; GBM: 1), whereas 6 patients had a progressive disease (PD). The percentage of 1-year survival obtained in patients with SD was significantly higher than that found in patients with PD. Moreover, a clear improvement in mood, social relationships and pleasure perception was observed in 9/14 (64%) patients under OXY administration. These preliminary results would furtherly confirm the possibility to obtain a control of the neoplastic growth also in advanced cancer patients eligible for the only supportive care alone by simply correcting the main cancer- progression-related endogenous neuroendocrine deficiencies, including pineal hormones, endocannabinoid system and OXY secretion.

**KEYWORDS:** Cancer Progression; Cannabinoids; Oxytocin; Palliative Therapy; Pineal Hormones.

## INTRODUCTION

The recent advances in the knowledge of the neuroendocrine and immunological mechanisms responsible for cancer onset and development have allowed the discovery of the existence of several natural anticancer non-toxic molecules, either in plants or in the same human body, with the following possibility to offer new potential anticancer regimens with natural anticancer agents to cancer patients with disseminated neoplasms eligible for the only best supportive care (BSC) alone, even though not completely standardized, in an attempt to improve not only their quality of life, but the survival time by improving the efficacy of the anticancer immunity [1-3]. Most of the endogenous anticancer molecules are produced by the pineal gland, whose anticancer activity is known since many years, by representing one of the main organs responsible for the natural anticancer resistance of living organisms [4]. The main anticancer hormones produced by the pineal gland are the indoles melatonin (MLT) [5] and 5-methoxytryptamine (5-MTT) [6], and several beta-carbolines, the most investigated of them is the 6-methoxy-1,2,3,4-tetrahydro-beta-carboline [7], the so-called ***pinealine***. The pineal hormones play an anticancer activity due to several mechanisms, including a direct cytostatic cytotoxic activity, an immunostimulating effect on the T lymphocyte-mediated anticancer immunity, and an anti-angiogenic action [8]. The endogenous cannabinoids, the most important of them are consisting of arachidonyl-ethanol-amide (AEA) and 2-arachidonyl-glycerol (2-AG), have also appeared to exert an anticancer action on several cancer cell lines through a direct anti-proliferative and anti-angiogenic action [9], as well as by counteracting macrophage-mediated chronic inflammatory response, which has been proven to promote cancer dissemination [10]. The endogenous cannabinoids are destroied by the enzyme fatty acid amide hydrolase (FAAH), then the administration of FAAH inhibitors may allow an increase in cannabinoid endogenous content [11]. The non-psychoactive principle of Cannabis indica cannabidiol (CBD), which is not a cannabinoid receptor agonist, has appeared to inhibit FAAH activity [9], then its administration could allow an increase in the endogenous content of both AEA and 2-AG, with a following enhancement in the potency of the natural resistance against cancer growth. A potent anticancer activity is also played by the cardiac hormone atrial natriuretic peptide (ANP) because of its anti-proliferative, anti-angiogenic, anti-inflammatory and immunostimulatory effects [12], even though its too short half-life at present does not permit its clinical therapeutic use. Finally, the neurohypophyseal hormone oxytocin (OXY) has also appeared to be an anticancer molecule, at least against breast cancer, brain tumors, and gynecologyc neoplasms [13], due to a direct antiproliferative action [14] and to an immunostimulatory activity on IL-2-dependent anticancer immunity [15], whereas controversial results have been reported for prostate cancer and germinal tumors. According to the recent advances in the psychoneuroendocrinoimmunology (PNEI) of cancer, at present it is known that cancer progression and cancer-related immunosuppression may be due at least in part to a pineal endocrine deficiency [16], to a failure of the endocannabinoid system [9] and probably to a dimished OXY secretion [13]. Then, the progressive correction of these major cancer-related neuroendocrine deficiencies through an exogenous administration could improve the control of cancer growth. In fact, some preliminary clinical studies have already demonstrated the possibility to enhance the survival time in a considerable number of advanced cancer patients eligible for the only palliative therapy, and also to achieve some tumor regressions even though in a very low percentage of untreatable disseminated cancer patients, through the administration of high-dose pineal indole hormones MLT and 5-MTT [17]. Further studies have shown the possibility to achieve a greater increase in the survival time of untreatable



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cancer patients by the concomitant administration of cannabinoid agonists or CBD [18]. The present preliminary study has been performed in an attempt to establish whether the further concomitant administration of OXY may restablish a control of the neoplastic growth in untreatable cancer patients, who progressed after an initial disease stabilization under a neuroendocrine regimen with the only pineal indoles MLT and 5-MTT plus CBD.

## PATIENTS AND METHODS

The study included 14 consecutive patients (M/F: 4/10; median age 54 years, range 31-74). The experimental protocol was explained to each patient, and written consent was obtained. Eligibility criteria were, as follows: histologically proven solid tumor, measurable lesions, histological diagnosis of triple negative breast cancer (TNBC), brain glioblastoma (GBM), and gynecologic tumors, and untreatable tumor because of lack of response to the previous standard anticancer treatments and progression on a neuroendocrine schedule with the only pineal indoles plus CBD. All molecules were given orally. MLT and 5-MTT were administered at a daily dose of 100 mg and 10 mg, respectively during the period of darkness and maximal light, corresponding to the times of their physiological circadian secretion. CBD was given at a dose of 10 mg twice/day (8 AM and 8 PM). Finally, OXY was administered at a dose of 2 mg twice/day (8 AM and 8 PM). The clinical response was evaluated according to WHO criteria. The immunobiological response was evaluated by determining lymphocyte-to-monocyte ratio (LMR), whose diminished value has appeared to predict a less favourable prognosis in most cancer histotypes [19], since it has been proven to synthetically reflect the equilibrium between the anticancer immunity mediated by TH1 and cytotoxic T lymphocytes and the chronic inflammatory status-related immunosuppression of the anticancer immunity, mediated by the macrophage and regulatory T lymphocyte (T reg) systems. Normal values of LMR observed in our laboratory (95% confidence limits) was more than 2.1. Data were statistically evaluated by the chi-square test and the Student's t test, as appropriate.

## RESULTS

The clinical results are reported in **Table 1**. Tumor histotypes were, as follows: TNBC: 4; GBM: 3; ovarian cancer: 3; cervix carcinoma: 2; endometrial adeocarcinoma: 2. No objective tumor regression was seen. However, a stable disease (SD) was obtained in 8/14 (57%), with a median duration of 5 months (range 3-11 months) (GBM: 1; TNBC: 2; ovary: 2; endometrium: 2; uterine cervix: 1), whereas the remaining 6 patients had a progressive disease (PD). Moreover, the percentage of SD was significantly higher in patients, who had obtained a tumor regression or SD in response to the previous same neuroendocrine regimen without OXY than in those who had a PD (6/8 (75%) vs 2/6 (33%), P<0.05). A survival longer than 1 year was achieved in 7/14 (50%) patients, and the percentage of 1-year survival was significantly higher in patients, who obtained a SD than in those who had a PD (6/8 (75%) vs 1/6 (17%), P<0.01). Finally, the percentage of SD was higher in patients with normal pre-treatment values of LMR than in those with abnormally low values prior to therapy (4/6 (67%) vs 4/8 (50%) ), even though the difference was not statistically significant. In any case, LMR mean values observed after 3 months of therapy were significantly higher in patients with SD than in those who had a PD (3.1 +/- 0.4 vs 1.5 +/- 0.3, P<0.05). No objective or subjective toxicity was observed. In contrast, with respect to the already subjective benefits achieved by pineal hormones plus CBD, consisting of improved quality of sleep, relief of anxiety, asthenia, anorexia, cachexia, and improvement of mood, the further administration of OXY clinically allowed a clear improvement in the affective and emotional relationships and pleasure perception in 9/14 (64%) patients, and the percentage of improvement was significantly higher in patients with SD than in those with PD (7/8 (88%) vs 2/6 (33%), P<0.05).

**Table 1**: Clinical results with the pineal hormones melatonin (MLT) and 5-methoxytryptamine (5-MTT) plus cannabidiol (CBD) and oxytocin (OXY) in untreatable cancer patients progressing on pineal hormones and CBD alone.

| Cases | Sex | Age | Tumor* | Metastases | Response** | Duration (months) | Survival (months) |
|---|---|---|---|---|---|---|---|
| **1** | F | 54 | Ovary | Liver, perito-neum | SD | 8 | 15 + |
| **2** | F | 61 | Endometrium | Lung | SD | 5 | 10 |
| **3** | F | 72 | TNBC | Brain, liver | PD | - | 5 |
| **4** | M | 66 | GBM | - | PD | - | 4 |
| **5** | F | 71 | Endometrium | Peritoneum | SD | 11 | 15+ |
| **6** | M | 58 | GBM | - | SD | 5 | 9 |
| **7** | F | 41 | TNBC | Liver, lung | PD | - | 3 |
| **8** | F | 31 | Cervix | Nodes | SD | 5 | 18+ |
| **9** | M | 66 | GBM | - | SD | 3 | 7 |
| **10** | F | 74 | Ovary | Peritoneum | SD | 11 | 14+ |
| **11** | F | 71 | TNBC | Bone | SD | 8 | 16+ |
| **12** | F | 38 | Cervix | Lung | PD | - | 15 |
| **13** | F | 35 | TNBC | Liver | PD | - | 12+ |
| **14** | F | 38 | Ovary | Liver | PD | - | 3 |

*GBM: Glioblastoma; TNBC: Triple Negative Breastcancer; ** SD: Stabledisease; PD: Progressive disease

## DISCUSSION

The results of this phase-2 preliminary study seems to suggest that the administration of the neurohypophyseal hormone OXY may restablish a disease control in untreatable advanced cancer patients, who had already obtained a disease control and an increased survival under treatment with pineal indoles and CBD alone with respect to the simple BSC, including tumors which represent the most malignant ones within the human neoplasms, such as TNBC and GBM. This finding is not surprising since OXY, even though it is generally known for the only gynecologic reasons, has appeared to play a potential anticancer activity by direct cytotoxic action, an anti-angiogenic activity and a stimulation of the anticancer immunity [13-15]. Moreover, OXY has been proven to exert a fundamental role in the regulation of human affective, social and sexual relationships. Further studies will be required to establish whether the anticancer action of OXY may be mainly due to a direct antiproliferative activity, or to a concomitant immunostimulatory effect on the anticancer activity [15], as suggested by the evidence of higher LMR values in patients with disease control than in those, who progressed. Moreover, according to a neuroendocrine approach in cancer cure consisting of a progressive correction of the main cancer-related neuroendocrine deficiencies, further studies will be needed to evaluate whether an initial neuroendocrine regimen with pineal indoles, CBD and OXY allow better results with respect to those, which may be achieved by the only pineal indoles and CBD in advanced cancer patients eligibile for the only palliative therapy. The efficacy of OXY in improving social and affective relationships referred by a considerable number of patients with disseminated cancer would not be surprising, since it has been shown that OXY may regulate the activity of several brain areas involved in the modulation of emotional life by modulating the activity of amygdala [19] and stimulating the functionless of mirror neurons [20], whose fundamental role in learning and in promoting the human relationships is well known [21]. Morever, both cannabinoid and MLT may stimulate OXY secretion [22]. Therefore, brain cannabinoid system, pineal gland and OXY-secreting neurohypophysis would constitute a fundamental neurochemical system involved in both social and affective relationships and in natural resistance against cancer development and growth. In fact, cancer progression has been proven to be associated with a progressive concomitant decline in the functionless of the pineal gland, brain endocannabinoid activity and OXY secretion [5,9,16].

## CONCLUSION

Further randomized studies with pineal indoles plus CBD versus their association with OXY will be required to establish whether the concomitant administration of OXY may further increase the disease control and improve the quality of life in advanced cancer patients, for whom no other standard anticancer therapy may be available.

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