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Clinical Use of Cannabinoids in Cancer: A Phase-2 Study of a Rotatory Therapy with Cannabinoids in Association with Antitumor Pineal Hormones and Angiotensin 1-7 in Advanced Cancer Patients Eligible for the Only Best Supportive Care

Lissoni P*, Rovelli F, Messina G, Ceppodomo D, Monzon A, Sassola A, Poli F, Costantino G, Zecchinato F and Di Fede G

Institute of Biological Medicine, Milan, Italy

***Corresponding author:** Lissoni P, Institute of Biological Medicine, Milan, Italy; E-mail: paolo.lissoni@gmx.com

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Abstract

The recent advances in the investigation of cancer physiopathology have shown that tumour onset and growth may depend at least in part on a immunosuppressive status due to a progressive diminished function of natural anticancer structures, including pineal gland, endocannabinoid system, and ACE2-angiotensin 1-7 (Ang 1-7) axis, which are responsible for the natural anticancer resistance. In fact, preliminary clinical studies with the pineal antitumor hormones melatonin (MLT) and 5-methoxytryptamine (5-MTT), cannabinoids, and Ang 1-7 have been shown to achieve a control of the neoplastic growth also in cancer patients eligible for the only supportive care. At present, the most commonly used cannabinoids are represented by cannabidiol (CBD), cannabigerol (CBG), and palmitoyl-ethanol-amide (PEA). All these cannabinoids play an anticancer cytotoxic action, without any apparent difference in their antitumor efficacy. Therefore, according to the opioid rotation therapy, a rotatory schedule of administration of each single cannabinoid could delay the onset of tumour resistance against the cytotoxic action of cannabinoids. On these bases, a study of a rotatory therapy with the three main cannabinoids, CBD, PEA and CBG, in association with pineal indoles and Ang 17 was planned in advanced cancer patients eligible for the only supportive care. The study included 22 consecutive locally advanced or metastatic cancer patients affected by different tumour histotypes. All drugs were given orally, every day without interruption. MLT and 5-MTT were administered at 100 mg/day in the night, and at 20 mg/day in the early afternoon, respectively and according to their circadian secretion. The rotatory cannabinoid therapy consisted of the administration of each single cannabinoid for a duration of 40 days, starting with CBD at 20 mg twice/day being the more anxiolytic cannabinoid agent, followed by PEA at 600 mg twice/day, and finally by CBG at 20 mg twice/day. A disease control was achieved in 17/22 (77%) patients, with an objective tumour regression in 5/22 (23%). Moreover, the control of tumour growth was associated with an improvement in the immune status and in well-being of patients, with a relief of anxiety, pain, asthenia, nausea, and sleep disorders. The results of this study show that the reinduction of an adequate function of the three major antitumor human biological systems, consisting of pineal gland, endocannabinoid system, and ACE2-Ang 1-7 axis, through an exogenous administration of their molecules may control cancer growth also in patients, for whom no other standard anticancer therapy was available.

Keywords: Angiotensin; Cannabinoids; Melatonin; Neuro-immunotherapy; Opioids; Pineal gland

Introduction

Opioids and cannabinoids are commonly employed in the palliative therapy of cancer. Opioids are used since many years in the treatment of cancer-related pain [1], while the cannabinoid agents have been clinically introduced only more recently [2,3]. However, there is a great difference in their effects, since while the opioids are substantially used for the only therapy of pain, cannabinoids may be effective not only in the treatment of pain, but also of various other cancer-related symptoms, including cachexia, anorexia, anxiety, vomiting and muscle contractions. Moreover, while morphine and other mu-opioids are used for the

only palliative therapy because of their immunosuppressive action [4], cannabinoids may exert potentially antitumor effects [5]. Therefore, cannabinoid therapy of cancer could constitute the point of connection between palliative and curative therapies of human neoplastic diseases. Then, the major difference between opioids and cannabinoids in the treatment of cancer regards their effects on tumor growth itself. In fact, while opioids, particularly the mu-opioid agonists, may promote tumor growth by either exerting an immunosuppressive action on antitumor immunity by counteracting T cell proliferation and differentiation [4], or directly stimulating cancer cell proliferation [6], cannabinoids may act as potential natural anticancer agents [5]. Then, the clinical use of cannabinoid instead of opioids in the palliative therapy of cancer is justified by their efficacy in the therapy not only of pain, but also of other symptoms, mainly cachexia and vomiting, as well as because of their potential anticancer activity and complete lack of immunosuppressive effects on the anticancer immunity. In fact, even though at present they have been clinically used substantially for the only palliative therapy of cancer, cannabinoids may also play an anticancer activity through several mechanisms, including direct cytotoxic action, inhibition of angiogenesis, and block of the secretion of pro-tumor inflammatory cytokines [5], including IL-6, TNF-alpha, and mainly IL-17 [7], which may directly stimulate cancer cell proliferation, by representing one of the main pro-tumoral cytokines. In addition, the lack of efficacy of some antitumor therapies, including cancer immunotherapy with monoclonal antibodies, has appeared to be due to an enhanced IL-17 secretion [9]. Then, the inhibition of IL-17 secretion could improve the efficacy of host anticancer immunity. In any case, it has to be remarked that mu-opioid drug-induced immunosuppression may change in relation to the type of agent, and in particularly it has been shown that the greatest immunosuppressive effect is played by fentanyl, while hydromorphone and oxycodone would not exert suppressive effects on the antitumor immunity [10]. By synthetizing, opioid and cannabinoid agents may be either synergic, or opposite in their therapeutic effects. In more detail, opioid and cannabinoid drugs are synergic in the treatment of pain [11], whereas they are opposite in the therapy of vomiting and anorexia, but they are primarily opposite in their influence on tumor growth, promoted by opioids and counteracted by cannabinoids. Delta and kappa opioids may exert both stimulatory and inhibitory effects on the anticancer immunity, depending on those and schedule of administration [12]. In addition. Oxytocin may also exert antalgic effects [13], and it would play a fundamental role in the regulation of connections between brain opioid and cannabinoid systems. Moreover, even though the mechanism has to be better explained, from an empiric point of view it has been demonstrated that the antalgic action of opioids and the duration of their effects across the time without the need to increase their dosage because of the occurrence of tolerance may be amplified by a rotation administration of the different mu-opioid agonists [14], by changing the type of the opiate drug across the time. On the contrary, at present it is not known whether a same conclusion may be proposed for an eventual cannabinoid rotatory treatment, not only to prolong their antalgic activity, since the mechanism of tolerance is not relevant for cannabinoids, but also to enhance their potential anticancer action by opposing the occurrence of tumor resistance to each potential antitumor molecule through a rotatory administration of the different cannabinoid agents. At this proposal, from a pharmacological point of view the cannabinoid agents may be subdivided into two major classes [2,3], consisting of cannabinoid receptor (CB) 1 and 2 agonists, and inhibitory of fatty acid amide hydrolase (FAAH), the enzyme involved in cannabinoid catabolism, with a consequent increase in the endogenous content of cannabinoids (4). In any case, both classes of cannabinoids have appeared to exert a direct anticancer activity [4]. Within the Cannabis plant, the only CB1-CB2 receptor agonist, then provided by psychotropic effect, is tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabigerol (CBG) are the main FAAH inhibitors, while cannabinol (CBN) may act as partial CB1 receptor agonist. The affinity for CB receptor of CBG is greater than that of CBD, then the less anxiogenic factor of Cannabis is CBD. On the other hand, the CB1-CB2 receptor agonists of the human endocannabinoid system consist of arachidonyl-ethanol-amide (AEA), also termed anandamide, and 2-arachidonyl-glycerol (2-AG), while the most investigated endogenous FAAH inhibitor is represented by palmitoyl-ethanol-amide (PEA) [4]. In addition, previous preliminary clinical studies have shown that the administration of cannabinoid agents from Cannabis in association with potential endogenous anticancer hormones, such as the pineal indoles melatonin (MLT) [15] and 6-methoxytryptamine (5-MTT) [16], and the enzymatic product of ACE2, the angiotensin 1-7 (Ang 1-7) [17], may control tumor growth also in advanced cancer patients, who failed to respond to the common standard anticancer treatments [18,19]. On these bases, a study was planned to evaluate the clinical effects of a rotatory therapy with three different cannabinoids, consisting of CBD, PEA, and CBG in association with the pineal hormones MLT and 5-MTT, plus Ang 1-7 in advanced cancer patients, who failed to respond to the standard anticancer treatment, then suitable for the only palliative therapy, according to previous preliminary clinical studies [18,19].

Patients and Methods

This phase-2 study include 22 consecutive advanced cancer patients, who failed to respond to the conventional anticancer therapies, including chemotherapy, radiotherapy, targeted therapy, anti-angiogenic therapy, and immunotherapy, or who has

poor clinical conditions, which made them as unable to tolerate the common oncological treatments, then suitable for the only best supportive care. After the approval of the Ethical Committee, the clinical protocol was explained to each patient, and written consent was obtained. Eligibility criteria were, as follows: histologically proven solid neoplasm, measurable lesions, locally advanced or metastatic disease, lack of response to the previous standard anticancer treatments and no availability of other standard antitumor therapies, or poor clinical conditions unable to tolerate the conventional therapies, no double tumor, life expectancy less than 1 year, and no concomitant standard anticancer therapy.

Table 1: *Clinical Response (WHO Criteria) In a Group of 22 Untreatable Advanced Cancer Patients with Pineal Hormones, Cannabinoids, and Angiotensin 1-7.*

CLINICAL RESPONSE*	CR	PR	CR + PR	SD	DC	PD
	1	4	5 (22%)	12	17 (77%)	5
*CR: Complete response; PR: Partial response; SD: Stable disease; DC: Disease control; PD: Progressive disease.						

Table 2: *Changes in lymphocyte-to-monocyte ratio (LMR) (mean +/- SE) in advanced cancer patients in relation to their clinical response.*

CLINICAL RESPONSE	n	LMR	
		BEFORE THERAPY	AFTER THERAPY
OBJECTIVE TUMOR REGRESSION	5	2.6 +/- 0.4	4.5 +/- 0.2*
STABLE DISEASE	12	2.3 +/- 0.3	3.3 +/- 0-5
PROGRESSIVE DISEASE	5	1.1 +/- 0.2	0.8 +/- 0.1
			*P< 0.025

Tumor histotypes were, as follows: breast cancer: 8 (triple negative breast cancer:3); lung adenocarcinoma: 4; pancreatic adenocarcinoma: 3; gastric cancer: 3; colorectal carcinoma: 2; biliary tract carcinoma: 1; mesothelioma: 1: Distant organ metastases were present in 21/22 (95%), and dominant metastasis sites were, as follows: nodes: 3; bone: 1; lung: 8; liver: 6; lung plus liver: 2; peritoneum: 1. All drugs were administered orally. MLT was given at 100 mg/day in the evening, generally 30 minutes prior to sleep. The other pineal indole, the 5-methoxytryptamine (5-MTT) [17] was given at 20 mg/day during the period of maximum light. Cannabinoids were given twice/day (8 AM and 8 PM) according to a rotatory schedule of a duration of 40 days/each, starting with CBD at a dose of 20 mg twice/day being the most anxiolytic one [14-16], followed by PEA at a dose of 600 mg twice/day, and after by CBG at a dose of 20 mg twice/day, followed by a new rotatory cycle, starting again with CBD. Finally, Ang 1-7 was given at a dose of 0.5 mg twice/day in gastro-protected capsules because of its peptidergic nature. The treatment was continued every day without interruption until disease progression. To evaluate the clinical response, which was assessed according to WHO criteria, the radiological examination, including CT scan, MR and PET, were repeated at 3-month intervals. The immune status of patients was evaluated by determining at 1-month intervals the lymphocyte-to-monocyte ratio (LMR), since the evidence of abnormally low values of LMR has appeared to predict a poor prognosis and a lower survival [20]. Normal values observed in our laboratory (95% confidence limits) was below 2.1. Data were reported as mean +/- SE, and statistically analyzed by the chi-square, the Student's t test, and the analysis of variance, as appropriate.

Results

The clinical results were reported in (Table 1). A complete response (CR) was obtained in 1/22 (5%) patients, who was affected by peritoneal metastases due to gastric cancer. A partial response (PR) was achieved in other 4/22 (18%) patients (lung adenocarcinoma: 2; common breast cancer: 1; triple negative breast cancer: 1). Then, an objective tumor regression was obtained in 5/22 (23%) patients. A stable disease (SD) was observed in 12/22 (55%) patients, with a consequent disease control (DC) in 17/22 (77%) patients, whereas the remaining 5/22 (23%) patients had a progressive disease (PD). The median duration of DC was 8+ months (range 5 – 38+). No therapy-related toxicity occurred. On the contrary, most patients experienced a clear subjective improvement of their well-being, particularly in mood, quality of sleep, and relief of asthenia. CBD was apparently more effective in the treatment of nausea and vomiting, but no particular superiority of one cannabinoid agents with respect to the others in the treatment of some symptoms was noted. Finally, the control of cancer growth was associated with

an improvement of the anticancer immunity, as shown by considering changes in LMR mean values. In fact, as reported in (Table 2), LMR men values significantly increased on therapy in patients, who achieved a complete or partial tumor regression. On the contrary, LMR enhanced in patients with SD, whereas it decreased in those with PD, even though none of these differences was statistically significant. In more detail, abnormally low pre-treatment values of LMR were seen in 9/22 (41%), and pre-treatment LMR values observed in patients who had a PD were significantly lower than those found in patient with tumor regression or SD ($P< 0.01$). Moreover, a normalization of LMR values on treatment was achieved in 5/9 (61%) patients. In addition, the percentage of LMR normalization observed in patients with CR or PR was significantly higher with respect to that found in both patients with SD (2/2 (100%) *vs* 3/12 (25%), $P<0.05$) or PD (2/2 *vs* 0/5, $P< 0.01$).

Discussion

According to previous clinical data [18,19], the results of this study furtherly confirm the possibility to counteract tumor growth also in advanced cancer patients, who failed to respond to the standard antitumor medical oncological therapies, by the administration of natural anticancer molecules, most of them originate from human body itself, including pineal hormones, cannabinoids, and Ang 1-7. Moreover, the results of this study with a rotation cannabinoid therapy seem to be superior with respect to those reported in previous clinical investigations by using only one single cannabinoid agent, including CBD, CBG, or PEA [2-19]. This evidence would confirm the possibility to opposite the onset of tumor cell resistance against the cytotoxic action of the different cannabinoids. However, the relatively low number of patients and the different tumor histotypes do not allow us to draw define conclusions about the possible greater clinical activity of a rotatory schedule of cannabinoid administration with respect to the administration of the sane cannabinoid agent for a long period of time. Moreover, further studies by monitoring changes in antitumor and pro-tumor cytokine blood levels and other immune parameters will be required to better define the immune variations occurring on therapy. In any case, the results of this study justify further randomized clinical investigations with a single cannabinoid agent versus a rotatory schedule of administration of the main commonly used cannabinoids in relation to the different cancer histotypes. Moreover, further studies will be needed to better define the subjective effects of each single cannabinoid agent, particularly in terms of relief of pain and anxiety.

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