

What are the perspectives of cannabidiol (CBD) for the treatment of glioblastoma?

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Glioblastoma (GBM) or WHO grade IV astrocytoma is the most aggressive form of brain tumors and ranks among the deadliest types of cancer. It is also the most common malignant primary brain tumor. Its high proliferation rate and invasiveness, together with a considerable cellular and molecular heterogeneity, is a challenge for treatment. Current therapeutic strategies include surgery, chemotherapy, radiotherapy and combinations thereof. Temozolomid (TMZ) is considered as the benchmark for treatment but resistance to TMZ antitumoral action is frequent and contributes to the overall poor prognosis. After second line treatment with TMZ, median survival is around 5.1 to 13 months, depending on the study [1].

Anti-cancer effects of cannabinoids have long been argued. Scientific evidence goes back to 1974 at the Medical College of Virginia at the behest of the US government. In an attempt to provide data proving a link between cannabis and cancer risk in order to provide evidence justifying international prohibition, the contrary was observed [2]. With the detection of the endocannabinoid system in the early 90ies, much insight was gained into the mechanisms of cannabinoids; a number of preclinical studies, *in vitro* as well as *in vivo*, confirmed the antineoplastic properties of both, phyto- and synthetic cannabinoids. Out of the phytocannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the best studied substances. These two cannabinoids differ in their effective doses: Common oral doses of THC are in the order of two to three times 2.5 mg to 10 mg/day, whereas CBD is currently administered in a dose of 100 to 300mg twice daily; doses up to 1,500mg CBD have been well tolerated. THC has some inherent clinical drawbacks due to its psychotropic properties, in addition to increased anxiety and withdrawal symptoms after high doses and down-regulation of CB1 receptors [3,4]. In contrast, CBD is free from such constraints. Furthermore, THC is unsuited for children and adolescents. Although rare when compared with adults, brain tumors are the most common solid tumors in children.

Cannabinoids demonstrate tumor-specific cytostatic/cytotoxic effects modulating the growth of glioblastoma by multiple, often overlapping mechanisms that repeatedly showed synergism when combined with other treatments. In particular CBD has been reported to activate apoptosis via oxidative stress (increase in ROS production in tumor cells [5]), and to inhibit tumor cell proliferation by inducing cell cycle arrest. Furthermore, CBD inhibits tumor angiogenesis and infiltration/ invasion even at low concentrations and abrogates resistance of glioma stem-like cells to BCNU (carmustine) therapy [6]. Cannabinoids are synergistic with chemotherapy and also with gamma-irradiation [7-9]. So far, experiments suggest that high doses of cannabinoids are necessary in order to achieve anti-tumor effects. In the inverse, low concentrations or doses respectively, may even enhance the growth of glioma, lung and breast cancer cells *in vitro*

[10] and *in vivo* [11,12]. In addition to the tissue concentration and experimental conditions, effects depend very much upon the nature of the tumor cells. Although preclinical results cannot be transferred one-to-one to the situation in man, dose-dependency has been observed not only *in vitro* but also in animal experiments. A condensed overview on available *in vivo* results with CBD is presented in table 1.

As can be seen, all experiments used relatively high doses of cannabinoids and all reported a significant effect on tumor growth and/or survival; in one experiment, one of five animals were even completely free of cancer after receiving 15 mg CBD/kg [13].

In man, results of glioblastoma treatment with cannabinoids are still limited and restricted to the pioneering study of Guzman et al. [15] with THC, and a recent phase I/II - study that administered nabiximols, a 1:1 combination of two refined extracts, each containing around 65–70% CBD or THC respectively, as add-on treatment to TMZ [16]. In the first study, THC was infused into the resection cavity of nine freshly operated patients with treatment-resistant glioblastoma. Overall, the initial dose of THC administered to the patients was 20 to 40 mg at day 1, increasing progressively for 2 to 5 days up to 80 to 180 mg/day which corresponds to a very high, local dose. Most interesting, in those five patients that received more than one cycle (median duration per cycle: 10 days), three patients demonstrated a temporary reduction of tumor proliferation.

In the second study, patients with recurrent glioblastoma received a combination of CBD/THC up to a maximum tolerated dose (maximum 12 sprays per day, i.e. up to 30mg CBD + 32.4 mg THC per day) or placebo, in combination with dose-intensive TMZ. The one-year survival rate was significantly higher (83%) in the group that received nabiximols (12 patients) compared to the placebo-group (9 patients, 53% survived). Median survival was over 550 days compared to 369 (i.e. + 6 months). There is reason to assume that a higher ratio in favor of CBD such as 4/1 to 5/1 (CBD/THC) could achieve similar, may be even better results with a better tolerance as has been suggested by a very recent animal study [17]. With respect to the difference in effective doses between CBD and THC mentioned above, this animal experiment could be particularly relevant for man.

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Table 1. Results of CBD and CBD: THC combinations in animal models of glioma

Treatment	Model	Results	Ref.
CBD peritumoral, ~25mg s.c./kg/d, 5d /w for 23 d,	U87MG astro-cytoma s.c. xenograft, 8w old nude mice	~70% regression at day 18, but ~50% regression at day 23/end;	[12]
CBD + THC (each ~2 mg i.p./kg) on day 9, 13, 16 after tumor implantation; X-ray (4 Gy) on d9; CBD-BDS (63.5% CBD, 3.6% THC, 5.2% CBC) or THC-BDS (65.4% THC, 0.4% CBD, 1.8% CBC)	mouse glioma GL261 cells, orthotopically implanted, C57BL/6 mice (~9w old)	85% decrease of tumor volume and of vascularisation on d21 (animals sacrificed); CBD + THC reduced progression, further enhanced by irradiation (stagnant tumor sizes throughout the experiment); X-rays alone had no dramatic effect; <i>In vitro</i> effects (human glioma cell lines T98G, U87MG, mouse glioma GL261) differed: THC-BDS was more efficacious than THC-P; conversely, CBD-P was more efficacious than CBD-BDS; pretreatment of cells with THC-P + CBD-P together for 4 hours before irradiation increased radiosensitivity (P-pure > 96%)	[8]
CBD 15 mg i.p./kg, 5 days/w	athymic, GSC-bearing nu/nu mice	significant increase in the survival; initial response to CBD (reduction of tumor size at d22), followed by tumor resistance 1w later, d 29)	[5]
CBD, 15 mg i.p./kg, 5 d/w for 28 days	U251 glioblastoma cells, intracranial xenograft, mice	~95% decrease of tumor area; in 1/5 mice treated no tumor cells were observed in any of the brain regions analyzed;	[13]
CBD or THC 7.5 mg /kg/d; or CBD + THC 7.5mg each/kg/d; or 15mg THC/ kg /d; or CBD+THC each 3.7 mg/kg/d + TMZ 5 mg/kg/d, peritumoral, 15d	human glioma U87MG or T98G cells, s.c. xenograft, nude mice	7.5mg CBD/kg was slightly more effective than 7.5mg THC/kg; THC + CBD (each 7.5 mg/kg) was most effective and similar to 15mg THC/kg; tumor volume was stable on day 14 and 15; further enhancement by combination of THC with 5mg TMZ/kg; the triple combination of THC, CBD, and TMZ strongly reduced the growth of glioma xenografts and overcame the resistance to TMZ antitumoral action	[14]

BDS: Botanical Drug Substance (extract); B.W: Body Weight; CBC – Cannabichromene; d: day; GIC - Glioma Initiating Cells; exchangeable with GSC: Glioma Stem Cells; i.p.: intraperitoneal; nu: nude; s.c.: subcutaneous; TMZ: Temozolomide; w: week

In addition to the antineoplastic action, CBD has been reported to reduce nausea and/or vomiting [18], as well as having anti-depressive and analgesic properties. A very recent case series on glioma patients confirmed these effects [19].

In summary, combination of various anticancer regimens that include cannabinoids seems to be at present the most promising strategy for the treatment of glioblastoma and for improving the survival of patients. The large therapeutic range and excellent tolerance makes CBD an interesting substance for combination with temozolomide, radiation and/or other cannabinoids.

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