

## Cannabidiol May Prolong Survival in Patients With Glioblastoma Multiforme

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**Abstract.** *Background: Glioblastoma multiforme (GBM) is a relatively rare type of brain tumour with an incidence rate around 6 per 100,000. Even with the widely practiced combination of radiotherapy with adjuvant temozolomide, the median overall survival remains low with just 13.5 to 16 months after diagnosis. Patients and Methods: We retrospectively reviewed the survival of a cohort of 15 consecutive, unselected patients with histopathologically confirmed glioblastoma multiforme (GBM) who received CBD (400 to 600 mg orally per day) in addition to standard therapy (maximum resection of the tumour followed by radio-chemotherapy). Results: Of 15 patients, seven (46.7%) are now living for at least 24 months, and four (26.7%) for at least 36 months. This is more than twice as long as has been previously reported in the literature. The mean overall survival is currently 24.2 months (median 21 months). Conclusion: CBD is a well supported co-medication and seems to prolong the survival of patients with glioblastoma multiforme.*

Brain tumours are relatively rare in adults with an incidence in the order of 10 to 20 per 100,000. Over 120 types of brain tumours are known, of which glioblastoma multiforme

(GBM) not only have the worst prognosis but are also the most frequent with an age-standardised incidence rate of ~6 per 100,000. For many years, the standard management has been maximum surgical resection followed by adjuvant radio-chemotherapy. Even with the widely practised combination of radiotherapy with adjuvant temozolomide (1), the median overall survival remains low with just 13.5 to 16 months after diagnosis, and with a rate of only 4% to 5.8% of patients surviving for 5-years (2, 3). Prognosis varies with tumour location, extent of surgical removal, age at diagnosis and tumour type, but is also influenced by molecular factors (e.g., EGFR variants, IDH1-, IDH2-mutations, MGMT-inactivation, and/or a 1p/19q co-deletion), and microvascular density (4). Thus, although morphologically similar, different GBM tumours may translate into different clinical outcomes.

Cannabis has been used for palliative care in cancer patients for thousands of years, primarily to alleviate pain, as well as to improve quality of life in terminal stages of diseases including cancer. The two main cannabinoids produced by the plant are delta-9-tetrahydrocannabinol (THC, synthetic form: dronabinol) and cannabidiol (CBD). In contrast to THC, therapeutic doses of CBD are not psychotomimetic; therefore, CBD is not a scheduled drug. It does not activate or down-regulate CB1 receptors and does not produce tolerance when used over longer periods and in higher doses. Pure CBD differs from the so called “CBD-oils” which are more or less well-defined hemp extracts, most often lacking not only standardisation beyond their content of CBD and THC but also adequate quality control (5-7). This makes comparisons and assessment of results difficult, as a specific product cannot be easily replaced by another. Most extracts are therefore unsuitable for a reproducible, consistent medical treatment, even if many of them are popular for self-medication or as wellness products.

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Cannabinoids, particularly CBD, exhibit antiproliferative effects against a wide range of tumour types such as breast, cervix, colon, endometrium (8), glioma (9), leukaemia, lung, melanoma (10), neuroblastoma (11, 12), ovary, prostate, pancreas (12-14), and thyroid cancer cells (10, 11, 15, 16). Healthy cells were not affected in contrast to carcinoma cell lines (17). Despite of encouraging antineoplastic results that have been reported since 1975 (18), the potential antitumour activity of cannabinoids remained neglected until the detection of the endocannabinoid system (ECS) in the 90s; clinical data in cancer continue to be remarkably rare.

## Patients and Methods

All patients had histopathologically confirmed glioblastoma multiforme (WHO grade IV) and received pharmaceutical grade phyto-cannabidiol (CBD) in addition to standard treatment (maximum surgical resection followed by adjuvant radio-chemotherapy). Pharmaceutical CBD has been freely available for magisterial prescription for many years in several countries, *e.g.*, in Austria, Germany and Switzerland. In some cases, treatment is also reimbursed by the national social insurance. Phyto-CBD also received marketing authorisation in the United States already in June 2018 and in the European Community in September 2019.

For concomitant treatment of tumour patients, CBD was mainly administered as capsules (containing 100 or 200 mg of phyto-CBD of 99.8% purity; Trigal Pharma GmbH, Vienna) which were provided as magisterial preparations by an Austrian pharmacy; formulations were in compliance with the "Deutscher Arzneimittel Codex" (DAC). The local ethics committee and all patients consented to the treatment with CBD. Treatment was in conformity to national and institutional laws.

In 2019 we have already presented a consecutive case series of patients with brain tumours that have been treated with CBD concomitant to standard therapy (19); at this time, five of six patients with glioblastoma multiforme (GBM) were still alive. Here we present a retrospective analysis of these six patients, including nine new cases which allow a more accurate assessment of the overall survival.

## Results

### Case presentations

Case 1 is a male patient of 40 years old. In 2015, a left temporal glioblastoma multiforme grade IV (GBM), was diagnosed following epileptic seizures and removed. Thereafter, treatment with bevacizumab, lomustine (CCNU) and radiotherapy (Tumour Treating Fields) was started. Epilepsy was treated with levetiracetam. CBD (400 mg p.o./day) was started in May 2017. Since introduction of CBD, no further epileptic seizures have occurred. The tumorous formation marginally decreased and remained stable until July 2019 when a new lesion in the area of the hippocampus/hypothalamus has been detected by the regular magnetic resonance imaging (MRI) control. The patient passed away in January 2020, 51 months after diagnosis.

This patient was included already in the earlier case series (19) when he was still alive.

Case 2 is a male patient, 57 years old. A GBM located in the fronto-temporal, fronto-parietal region of the brain was partially resected. Radiochemotherapy after Strupp was started one month later, in October 2018, and continued until 2019. In August 2019 the MRI control demonstrated a marginal increase of the remaining tumour, and treatment with CBD (400 mg/day) was introduced. The patient finally died in June 2020 following to the progression of the tumour, 21 months after the diagnosis.

Case 3 is a male patient. He was operated on a frontally located GBM in January 2019 (MGMT methylated, no IDH mutation). Radiochemotherapy (CeTeG-scheme) (20) was started five weeks later, followed by treatment with temozolomide (150 mg/qm) for a total of 12 cycles. In August 2019 CBD (600 mg/day) was added to the current therapy. The condition of the patient was stable at his last control in December 2020 and is still alive.

Case 4 is a male patient diagnosed at 60 years of age. Following an epileptic seizure, computed tomography and MRI revealed a tumour mass located at the right side of the temporo-occipital lobe. A craniotomy in February 2019 demonstrated the presence of a grade IV glioblastoma multiforme with 50% necrotic tissue [ATRX preserved, IDH1 not mutated, p53 strongly positive, MIB-1 (Ki-67) positive (highly proliferating, ~40%) and positive for GFAP, EGFR]. Five weeks later, the patient was re-operated in order to remove residual, progressive tumour tissue. At the end of February, two weeks before the 2nd craniotomy, CBD was started (2x100 mg/day). From April 2019 onwards, the patient also received radio-chemotherapy with temozolomide. At the end of 2019, the tumour resumed growth, and the patient passed away in March 2020, 13 months after diagnosis.

This patient was included already in the earlier case series when he was still alive (19).

Case 5 refers to a male patient, diagnosed at 61 years of age. He presented with epileptic seizures in 2016 (controlled with levetiracetam). MR imaging showed a left mesio-temporal lesion. Craniotomy was preformed under ALA-control and a grade IV glioblastoma (MGMT hypermethylated, 1p19q-deletion) was partially removed in November 2016. Radio-chemotherapy was applied including temozolomide. Beginning in May 2017, comedication with CBD (2x200 mg/day) was started together with dronabinol (7.5 mg/day). The latest MRI demonstrated stable disease. Since the introduction of CBD, no further epileptic seizures have occurred. The patient was also included in the earlier case series; he is well and alive in March 2021, 51 months after partial resection of his tumour.

Case 6 refers to a male patient; at the age of five years the child had epileptic seizures. Further examinations revealed a

fronto-basal grade II astrocytoma, which was partially removed followed by radiotherapy. At the age of 41 years, in the end of 2017, the patient complained of reduced sensibility and slight paresis in the left arm and leg. In February 2018, a new mass (measuring 5×5×4 cm) in the right fronto-parietal lobe, straddling close to the pyramidal tract, was detected by MRI and partially removed two days later. Histology demonstrated a grade IV glioblastoma multiforme. Further molecular-pathologic examinations revealed a methylated MGMT gene promoter. At this time the old remaining fronto-basal tumour did not show any progression. Postoperatively, the patient received radiotherapy and temozolomide. A control MRI one month after craniotomy in March 2018 showed progression of the fronto-basal tumour, and CBD (2×200 mg/day) was started as comedication. A control (MRI) demonstrated a possible progression of the old, fronto-basal lesion which had not been irradiated after the intervention in February 2018, as well as changes on the recently operated lesion located in the right fronto-parietal lobe. Therefore, the patient was operated on again in August 2018. Following resection, this mass was diagnosed as necrotic/fibrotic; a typical coloration with 5-ALA was not observed. All MRI scans thereafter, until December 2019 demonstrated stable conditions. MRI scans in 2020 demonstrated a new, slowly growing subependymal lesion which was irradiated thereafter. The patient had been included already in the case series published earlier (19). He is still alive in March 2021, 37 months after his second craniotomy.

Case 7 refers to a male patient; at the age of 76 years a GBM located in the left-temporal area was partially resected in June 2018, and monotherapy with temozolomide was initiated but stopped after two months (replaced by avastin). After reoccurrence of the tumour the patient was reoperated in October 2019. CBD was started after the second craniotomy with 500 mg/day. The condition of the patient was stable until January 2020 when the tumour resumed growth. The patient finally died in October 2020, 28 months after the first surgical intervention.

Case 8 refers to a male patient with 66 years of age; in March 2017 the biopsy of an inoperable left fronto-temporal brain tumour revealed a GBM (ATRAX positive, IDH1-negative, with strong p53 expression). Surgical removal was not possible, and the patient was very ill, with a Karnofsky status of 70%. Treatment with fortectin and CBD (2×100 mg/day) was started one week later. He passed away 7 months after diagnosis.

Case 9 refers to a male patient diagnosed at 68 years of age. In February 2017 a right temporal tumour was partially resected. Histopathology demonstrated a GBM (IDH negative, 1p/19q available, MGMT methylated). Despite of the bad condition of the patient (Karnofsky index 40%), therapy with CBD (200 mg/day) was started three weeks later, with additional temozolomide, stopped after five days.

The tumour continued to grow, and the patient died in October 2017, 8 months after diagnosis.

Case 10 refers to a male patient. In June 2019, at the age of 54 years, a GBM located near the insula and operculum was partially resected (IDH1/H09 negative, MGMT not methylated) after the patient had complained of diminished right-sided sensibility and temporary loss of conscience. One month after resection, CBD was started (2×100 mg, increased to 2×300 mg/d three months later), with radiochemotherapy after Strupp in parallel. However, the patient died 14 months after surgery, end of August 2020.

Case 11 refers to a male patient diagnosed at 31 years of age of a left fronto-parietal GBM (craniotomy in March 2017; IDH-mutation, ATRX-protein missing, p53 negative, methylated MGMT-promoter). One week after surgery, CBD was started (2×300 mg/d), followed by radio-chemotherapy after Strupp. Since then, the condition of the patient is stable, and he is still alive as of March 2021, 47 months after craniotomy.

Case 12 refers to a female patient diagnosed at 49 years of age. In October 2018, a grade IV glioblastoma multiforme, (IDH1 negative, no loss of ATRX, expression of EGFR 10%), located at the right parieto-occipital lobe was partially removed, and radio-chemotherapy with temozolomide was started. In November 2018 CBD (2×200 mg/day) was added to the therapy. In February 2019 the patient was re-operated in order to remove the remaining, mainly necrotic tumour tissue. In an MRI at the end of July 2019, a slow progression of the remained temporo-parietal tumour mass was observed. The patient died 13 months after surgery.

This patient was included already in the earlier case series (19) when she was still alive.

Case 13 refers to a female patient diagnosed at 35 years of age. In December 2017, a right fronto-parietal grade IV glioblastoma multiforme was partially removed. Radio-chemotherapy with temozolomide was started thereafter. As the tumour was progressing, CBD (2×100 mg/day) was added to the treatment in March 2018. Over a period of 10 months a slight regression was observed. However, 11 months after diagnosis, the tumour resumed growth and the patient died two months later.

This patient was included already in the earlier case series (19).

Case 14 refers to a female patient, diagnosed (biopsy) at 56 years of age of an inoperable GBM (methylated MGMT-promoter), with a parieto-occipital, fronto-paramedian location in the right hemisphere in March 2019. Radiochemotherapy was initiated in April 2019 according to the CeTeG-protocol with lomustin-CCNU, 50mg/square meter and temozolomide 100mg/square meter. CBD (2×200mg/day) was added to the treatment in November 2019. Low dose dronabinol (7.5 mg/day) was added for a few weeks by the patient's family doctor. The patient is still stable and well in March 2021, 24 months after the diagnosis.

Case 15 refers to a male patient. Early in November 2019, at the age of 65 years, an intraaxial glioblastoma multiforme grade IV, sized about 7 cm × 6 cm × 5.5 cm, was diagnosed. Left-temporo-parietal resection was performed (IDH negative, ATRX not altered, EGFR strongly positive, MGMT moderately methylated, increased proliferation rate of 30-40%) and the tumour was removed as complete as possible. Thereafter, radiochemotherapy after Strupp was started (for a total of 6 cycles of temozolomide, radiation up to 60 Gray) to which CBD (400 mg/day) was added beginning in January 2020. Sixteen months after craniotomy the patient is very well and alive, with a Karnofsky index of 100%.

## Discussion and Conclusion

Taken together, the mean overall survival of this cohort of 15 consecutive, unselected patients with GBM and treated with CBD concomitant to standard therapy is currently 24.2 months (median of >21 months, 6/15 patients still being alive). This compares favourably with the median overall survival of >18 months (>550 days) observed in 12 patients treated with a fixed combination of CBD and THC (ratio ~1:1) plus dose intense temozolomide in a placebo-controlled clinical trial (21, 22). To note, the fixed CBD-THC combination cannot be compared directly with pure CBD used in our case series as it contains up to 35% of other pharmacologically active substances, such as terpenes and other cannabinoids. Two recent reviews reported two years overall survival rates of 18% (3) and 23.5% (23) respectively, and three years survival rates of 10.3% (24) and 11% (3). Out of the 15 patients of our cohort, seven (46.7%) are alive for at least 24 months, and four (26.7%) for at least 36 months which is more than two times longer. Considering only the subgroup of nine patients who have died in the meantime, the mean overall survival is still 18.5 months in our case series. The low number of patients and the fact, that concomitant treatment with CBD was not subject of a clinical study may limit the generalisation of our results. Nonetheless, overall survival is commonly considered as a hard endpoint.

Although these results with pure CBD are favourable, some important questions remain unanswered, in particular whether a combination of CBD with THC could increase survival. In a xenograft model (human glioma U87MG or T98G cells, nude mice) peritumoral injection of 7.5 mg CBD/kg was marginally more effective than 7.5 mg THC/kg. The addition of 7.5 mg CBD/kg to 7.5 mg THC/kg was most effective and similar to 15 mg THC/kg whereby the reduction of tumour volume was further enhanced by the addition of 5 mg temozolomide/kg (25). In a clinical setting, the therapeutic dose of a 1:1 combination of CBD and THC would be limited by the psychotomimetic and anxiogenic effects of THC; in contrast, CBD has been administered up to daily doses of 1,500 mg and was well supported (26).

Another, unresolved question concerns the most effective dose of CBD. A major goal in cancer therapy is to kill cancer cells via the natural process of apoptosis, avoiding eventual “recyclation” of cancer cells by autophagy. On a molecular basis, CBD is able to induce programmed cell death by autophagy as well as by apoptosis whereby the anti-proliferative effect has been related to the inhibition of the Ras/Raf/MEK/ERK pathway (26, 27). In vitro, a dose-dependent increase of apoptotic effects of CBD in glioblastoma and other human carcinoma cell cultures has been repeatedly reported (28-32) whereby the “apoptotic threshold” likely varies not only between different cancer cell types but also between cannabinoids (32-34). As might be expected, cell viability results are also highly dependent on the in vitro test conditions (*e.g.*, 2D versus 3D-cultures (29); or concentration of human serum (35)). Whereas cannabinoids such as THC or WIN55,212-2 demonstrate cytotoxic effects by acting on CB1/CB2-receptors, the anti-cancer mechanism of CBD is highly complex and still incompletely understood. A recent review identified 76 different molecular targets of CBD, most of them being ion channels/ionotropic receptors or enzymes (36). CBD is neither an agonist on CB1- nor on CB2-receptors but interacts with a wide range of ion channels known to play a role in carcinogenesis such as TRPA1, TRPM8, TRPV1, TRPV2, TRPV3, TRPV4, VDAC1, PPARs and the GPR55-receptor (34, 37, 38), among which TRPM8, TRPV1, TRPV2 and GPR55 are significantly higher expressed in GBM patients (39).

In conclusion, concomitant CBD seems to prolong the survival of patients with glioblastoma multiforme; CBD was well supported and did not cause side effects. Whether treatment with CBD could be optimised further by dose modulation and/or cannabinoid-combinations needs to be investigated.

## Conflicts of Interest

The Authors declare no conflicts of interest. GN works as independent consultant for physicians. Among others, he is consultant of the non-profit NGO “ICANNA”, the EIHA and a number of pharmaceutical companies. The Authors received no financial support for this case series.

## Authors’ Contributions

All Authors are aware of and approve the manuscript being submitted for publication. RL, MK, MS performed the clinical patient work. GN has consulted physicians on cannabinoids and has written the publication.

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