ANTICANCER RESEARCH *39*: 5797-5801 (2019)
doi:10.21873/anticanres.13783

Concomitant Treatment of Malignant Brain Tumours With CBD – A Case Series and Review of the Literature

RUDOLF LIKAR[1], MARKUS KOESTENBERGER[1], MARTIN STULTSCHNIG[2] and GERHARD NAHLER[3]

[1]*Department of Anaesthesiology and Intensive Care, Klinikum Klagenfurt am Wörthersee, Klagenfurt am Wörthersee, Austria;*
[2]*Neurological Department, Klinikum Klagenfurt am Wörthersee, Klagenfurt am Wörthersee, Austria;*
[3]*CIS Clinical Investigation Support GmbH, Vienna, Austria*

Abstract. *Grade IV glioblastoma multiforme is a deadly disease, with a median survival of around 14 to 16 months. Maximal resection followed by adjuvant radiochemotherapy has been the mainstay of treatment since many years, although survival is only extended by a few months. In recent years, an increasing number of data from in vitro and in vivo research with cannabinoids, particularly with the non-intoxicating cannabidiol (CBD), point to their potential role as tumour-inhibiting agents. Herein, a total of nine consecutive patients with brain tumours are described as case series; all patients received CBD in a daily dose of 400 mg concomitantly to the standard therapeutic procedure of maximal resection followed by radiochemotherapy. By the time of the submission of this article, all but one patient are still alive with a mean survival time of 22.3 months (range=7-47 months). This is longer than what would have been expected.*

Although relatively rare in absolute terms with an incidence of 3% of total cancer cases, brain tumours, in particular glioblastoma multiforme (GBM), rank among the deadliest diagnoses. GBM accounts for 12-15% of all intracranial tumours and 50 to 60% of astrocytic tumours. GBMs may manifest at any age, but mostly affect adults with a peak incidence between 45 and 75 years of age.

Brain tumours are on the rise. A recent random-effects model that analysed data from 1985 onwards found the overall incidence rate on all primary brain tumours to be 10.82 (95%CI=8.63-13.56) per 100,000 person-years (1). According to a prognostic estimation by the Austrian Ministry of Health, the incidence of brain tumours will increase by 84% for men and 26% for women between 2010 and 2030; death rates will nearly double (2). Similar results come from the UK where brain tumour incidence rates increased by 36% since the early 1990s (3).

Depending on the location and possibility for surgical removal, each type of tumour has its own biology and risks. Survival rates for malignant brain tumours vary widely, depending on the type of tumour, its grade and the location in the brain, with glioblastoma multiforme grade IV having the worst prognosis with a median survival of around 14 to 16 months (4). Only about 8 to 12% of patients survive two years.

Among the most important prognostic factors are age (with younger patients having a better prognosis), molecular factors (*IDH1, IDH2, MGMT*, and a 1p/19q co-deletion), and tumour location/extent of surgical resection (possibility for complete resection). A major focus of epigenetic research is DNA-methylation, which involves addition or removal of methyl groups on cytosines in cytosine-phosphate-guanine (CpG) dinucleotides and is involved in the regulation of gene expression. Although morphologically identical, different GBM tumours may translate into different clinical outcomes.

The primary aim of interventions is to increase survival and to maintain an acceptable quality of life. The standard treatment of GBM is maximal safe resection followed by adjuvant radiotherapy with concurrent chemotherapy. Temozolomide (TMZ) in combination with radiation therapy has been shown to increase the median survival of patients with newly diagnosed GBM by 2 to 3 months, from 12.1 (radiotherapy alone) to 14.6 months (5, 6). Following TMZ treatment after GBM recurrence, only 21% of patients obtain a progression-free survival (PFS) of six months and a six-month overall survival (OS) of 60% (7).

A number of preclinical studies suggest that phytocannabinoids might be effective in glioma therapy (8). Although

Correspondence to: Dr. Gerhard Nahler, CIS Clinical Investigation Support GmbH, Kaiserstrasse 43, 1070 Vienna, Austria. Tel: +43 152340150, Fax: +43 1523401599, e-mail: nahler@aon.at

Key Words: Cannabidiol, cannabinoids, chemoradiation, brain tumours, glioblastoma multiforme.

cannabis including extracts containing phytocannabinoids have been reported to reduce the growth of brain tumours in adults (9, 10) as well as in children (11, 12), a major lacuna in the use of herbal cannabis and "CBD-oils" is their poor standardisation, the lack of information on the exact composition, lack of comparability, lack of reproducibility and poor quality control (13). Nabiximols, a standardised, ~1:1 combination of two pharmaceutical grade extracts, one enriched with delta-9-tetrahydrocannabinol (THC), and the other with CBD, was shown recently to increase median survival of patients with recurrent glioblastoma multiforme by about 6 months, from 369 days (placebo group) to over 550 days when added to a dose-intensive temozolomide therapy (14).

In contrast, pure THC as well as CBD, are available as defined active pharmaceutical ingredients. Nonetheless, and despite of the promising preclinical data, reports on treatment of brain tumours with pure cannabinoids are very rare. In a pioneering study, THC was instilled into the resection cavity of patients with recurrent glioblastoma multiforme that had failed previous standard therapy (15). In this study, which did not aim to prolong survival, 5 of 9 patients received more than 1 cycle, and in 3 of these 5 patients, a temporary reduction in tumour proliferation was observed. However, the psychotomimetic properties of THC and down-regulation of CB1 receptors limit dosage and treatment duration. The recent report on the beneficial effects of non-psychotropic CBD in cancer patients is the most actual and the only demonstration of a possible anti-tumour effect of pure CBD in man (16).

Crystalline CBD, isolated from hemp or as a synthetic substance, is available with a purity of at least 98% (Deutscher Arzneimittel Codex DAC/NRF 2016/2, C-052, Avoxa-Mediengruppe Deutscher Apotheker GmbH, Eschborn, Germany) for magisterial prescription in some European countries such as Austria, Germany, Switzerland and the UK. A few companies provide CBD with a purity of 99.8% or higher. CBD is therefore a well-defined alternative to extracts or dronabinol (THC) for anti-tumour therapy. Furthermore, CBD has been reported to be well-tolerated and to reduce epileptic seizures (for which CBD received marketing authorisation by the FDA in June 2018), pain, nausea and to improve quality of life.

Herein, we report experiences with magisterial preparations containing pure (>99.8%) phyto-CBD (source: Trigal Pharma GmbH, Wien, Austria) prepared by a local pharmacy as adjuvant treatment of brain cancer patients. All patients consented to receive magisterial CBD capsules, and the local ethics committee has approved the treatment with CBD.

Case Presentations

Case 1, DI, female patient diagnosed at 38 years of age. In January 2018, an astrocytoma grade II located in the right post-central area was removed. Her medical history showed that her father as well as her grand mother died of a grade IV glioblastoma. Post-surgery, she specifically asked for no other treatment than CBD which was started 6 months after craniotomy, beginning on July 2018 (2×100 mg CBD/day for the first 2 weeks, then 2×200 mg/day). With CBD, her pain (numerical rating scale/NRS) was reduced from 4 to 0-1 within 2 months. Disease is stable at present.

Case 2, EJ, male patient, firstly diagnosed at 13 years of age. In June 1991 an oligoastrocytoma grade III, left occipital, was removed, followed by radio-chemotherapy until November 1992. In May 2015 a new, intraventricular tumour, an atypical grade II meningioma, was diagnosed and removed. The intervention was followed by a transient reduction in his vision on both sites. Because of a possible re-formation of tumour masses, CBD (2×200 mg/day) was started in August 2018. The patient is well, without new problems noted until now.

Case 3, GJ, male patient. In October 2015, at the age of 40 years, a left temporal glioblastoma multiforme grade IV, was diagnosed following epileptic seizures and removed. Thereafter, treatment with bevacizumab, lomustine (CCNU) and radiotherapy (Tumour Treating Fields) was started. Epilepsy is treated with levetiracetam. CBD (2×200 mg/day) was started in the end of May 2017. Since then, no further epileptic seizures have occurred. According to the latest magnetic resonance imaging (MRI) the tumorous formation is marginally decreasing.

Case 4, HB, female patient diagnosed at 44 years of age. In March 2016 an incomplete resection of a right temporo-basal grade II oligodendroglioma was performed. CBD was started in February 2017 and increased stepwise up to 2×300 mg one month later. The patient received levetiracetam as an antiepileptic therapy and intermittently also dronabinol, but no radio- or other therapy were received except analgesics on demand. The MRI in April 2019 showed stable disease.

Case 5, HW, 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), highly proliferating and positive for GFAP, EGFR). Five weeks later, the patient was re-operated in order to remove residual, progressive tumour tissue. In the end of February, two weeks before the 2nd craniotomy, CBD was started (2×100 mg/day). From April 2019 onwards, the patient also received radio-chemotherapy with temozolomide. At present, there is no sign of tumour recurrence. The patient also receives lacosamid/vimpat to prevent epileptic seizures.

Case 6, KE, male patient, age at diagnosis 61 years. He presented with epileptic seizures in 2016. MRI showed a left

mesial-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 (2×200 mg/day) was started together with dronabinol (7.5 mg/day). The latest MRI in February 2019 demonstrated stable disease.

Case 7, OB, male patient; at the age of five years the child had epileptic seizures. Further examinations revealed an fronto-basal astrocytoma grade II, which was partially removed, followed by radiotherapy. Follow-up examinations in 1993 showed no progression of the lesion. 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. An MRI in July 2018 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. All MRI scans thereafter, in November 2018, February 2019 and June 2019 demonstrated stable conditions.

Case 8, TG, 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 remained, mainly necrotic tumour tissue. At present, there is no sign of progression of the tumour.

Case 9, WC, 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 progressive, CBD (2x 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.

Discussion

Since 2016, nine consecutive patients with brain tumours have received pure CBD in addition to standard treatment (maximal surgical removal of cancer tissue and radio-chemotherapy). Treatment with CBD started with 100 mg twice daily and was increased usually to 200 mg twice daily after 2 to 4 weeks. Six of the nine patients were diagnosed with grade IV glioblastoma multiforme. Since diagnosis, all but one patients are still alive (mean survival time 22.3 months, range=7-47 months); one of them for almost four years, another for almost three years with no signs of progression or new lesions. The mean duration of treatment with CBD for these six patients was actually 17.5 months (range=7-28 months). Patient's quality of life and survival of this cohort is encouraging and seems to exceed the usual survival in comparable populations.

Dose of CBD and treatment schedule in our patients differed from the low-dose (average 2×10 mg/day, up to 60 mg/day), three days on/three days off schedule applied to cancer patients, as previously reported (16). Up to now, no systematic dose-effect study has been published; the optimal dose and treatment schedule for CBD remains to be elucidated. It may be dependent on the indication. Effects of CBD are very complex (13). Among other targets, CBD influences the levels of endocannabinoids such as of anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Doses of 800 mg CBD/day have been found to increase the AEA levels to approximately 1 pmol/ml after 28 days (17); steady state blood levels around 838-852 ng CBD/ml have been observed after a dose of 800 mg daily (18). Lower doses of CBD result in much lower blood levels (Cmax of 257-314 ng/ml after 250 mg, and ~1 ng CBD/ml after 5.4 mg CBD respectively; 18, 19). This is in the order where cannabinoids have been found, *in vitro*, to stimulate the growth of various cancer cells (20). Concerning AEA, an anticarcinogenic, concentration-dependent effect on glioblastoma cells was observed in micromolar concentrations (1 to 10 mcM) *in vitro*, and in picomolar doses per kg *in vivo* (21); AEA inhibited proliferation as well as cellular migration, and induced apoptosis in micromolar concentrations.

In animal cancer models, doses (administered mainly by intraperitoneal route) differed widely between 1 and 100 mg CBD/kg. To note, in animals, dosing is most often "rhythmic", with a 5-day on and a 2-day off treatment. At present, its synergistic effects with concomitant chemotherapeutic agents remains elusive. It was therefore prudent in our eyes to administer CBD doses known to be effective for other indications.

Many biological processes are subject of circadian (24 h) and/or circaseptan (weekly) rhythmicity, dosing at the most appropriate (but unknown) time of the day and/or rhythmic

dosing with days off may produce different outcomes than the "canonical" continuous dosing. In healthy adults, endocannabinoid blood levels demonstrate marked circadian rhythmicity with more than three times higher 2-AG levels around 12.00 to 13.00 in the afternoon than at 03.30 to 04.30 in the morning (22).

In diseased subjects, the endocannabinoid system is dysregulated. Although results were somewhat conflicting, AEA levels seemed to be lower and 2-AG levels were upregulated in glioblastomas (20). Glioma invasiveness has been linked to the tumour suppressor p38 MAPK; the anti-invasive effect of CBD interferes with this pathway (23). Increased expression and activity of p38 MAPK correlates with poor prognosis in glioblastoma multiforme. Intriguingly, the levels of phosphorylated p38 MAPK are significantly reduced in clock-deficient glioma cells, indicating that the circadian clock plays an important role in activation of this pathway (24).

In summary, preliminary observations suggest a potential role of CBD in the treatment of glioma whereby the optimal dose and dosing schedule remains to be elucidated.

Conflicts of Interest

There are no conflicts of interest to disclose regarding this study. The Authors received no financial support for this case series.

Authors' Contributions

RL, MK, MS performed the clinical patient work. GN consulted physicians on cannabinoids and wrote the manuscript.

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Received September 5, 2019
Revised September 17, 2019
Accepted September 18, 2019