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Case Report

Surprising Long Term Survival in Glioblastoma Patients Treated with Cannabidiol

Rudolf Likar[1] and Gerhard Nahler[2*]

[1]Abteilung für Anästhesiologie und Intensivmedizin, Klinikum Klagenfurt am Wörthersee, Klagenfurt am Wörthersee, Austria
[2]CIS Clinical Investigation Support GmbH, Wien, Austria

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ABSTRACT

Glioblastoma multiforme (GBM) is one of the most deadly tumors; even with aggressive radiochemotherapy, mean survival rates are only around 14 to 16 months post diagnose. Here we present the follow-up of 15 patients with GBM that have received concomitant cannabidiol (CBD) in addition to standard therapy, and that have been reported in details two years ago.

The survival time of patients is presented together with prognostic factors such as age at diagnose, molecular markers and dose of CBD.

The actual median survival time is 28 months, the arithmetic mean is 30.9 months, therefore about three to five times longer than expected. When comparing the group of patients surviving less than 28 months with those who lived longer, we found that all subjects who received a low dose of CBD (200mg per day) were in the group surviving less than 28 months. Apart from the daily dose of CBD, no striking difference was observed for other prognostic factors.

It is concluded that CBD contributed to the long term survival of GBM patients, and that this effect depends on the dose.

Introduction

Glioblastoma multiforme (GBM) is a very rare brain tumor with an actual incidence of about 3-4 in 100,000 people. It ranks among the most deadly tumors with mean survival rates around 14 to 16 months post diagnosis. Since many years, the first-line treatment for GBM is maximal resection followed by radiotherapy plus concomitant adjuvant temozolomide (TMZ) after Stupp [1]. Despite of aggressive therapy, only up to 18% of the patients are still alive two years, 11% three years, and around 4% five years after diagnosis [2]. Patients living longer than two years are frequently defined as "long term survivors". Although patients surviving 20 years have been reported, such cases are extremely rare [3].

The formation of GBM is a complex pathological process whereby, among other molecular modifications, a dysregulated methylation of DNA and histone modifications (e.g., methylation or acetylation/deacetylation) plays a role [4]. DNA methylation in GBM is characterised by the transfer of a methyl group donated by S-adenosylmethionine, mainly onto the C5 position of the cytosine to form 5-methylcytosine (5mC); it is a critical regulator of transcription, thus of tissue homeostasis and organ development [5]. If this happens in promoter ("regulatory") regions it is usually associated with gene silencing of transcription, while methylation in other, non-regulatory, transcriptional regions of the gene ("gene bodies") induces an increase or decrease of transcription. This process is catalyzed by a family of enzymes called DNA methyltransferases. Although basically reversible, methylation may be fixed, and can then govern persistent patterns of gene regulation. DNA methylation is subject of epigenetic influences and responsive to a wide range of substances including environmental toxins such as bisphenol A (released from plastic containers), or epigenetic changes induced by per- and polyfluoroalkyl substances (PFAS), widely used and persisting in the environment, or endocrine disrupting compounds (EDCs) such as triclosan, widely used as antibacterial and antifungal agent in hygiene products [6, 7]. Taken

Correspondence to: Gerhard Nahler, CIS Clinical Investigation Support GmbH, Kaiserstrasse 43, 1070 Wien, Austria; Tel: +43152340150; Fax: +431523401599; E-mail: nahler@aon.at

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together, GBM may be the overall result of many factors including epigenetic modifications.

It seems that certain molecular aspects favour long term survival of glioblastoma patients among which MGMT promoter methylation (of the gene coding for O6-methylguanin-DNA-methyltransferase) and IDH mutations (of the gene coding for isocitrate dehydrogenase) are the most relevant, in addition to more general factors such as the possibility for safe, maximal surgical resection and younger age (below 40 years). The transcription product of the MGMT gene is the DNA repair enzyme O6-methylguanin-DNA-methyltransferase that helps the tumor to repair the chemotherapy-induced DNA damage. Its expression decreases therefore the effect of alkylating chemotherapeutics such as TMZ. Conversely, silencing by methylation re-establishes efficacy of chemotherapy. Beside MGMT promoter methylation, IDH mutations are also considered as favourable prognostic factors, particularly when they are paired with MGMT methylation. The mutation of IDH1 results in the production of 2-hydroxyglutarate that can inhibit DNA- and histone-demethylating enzymes. Among the many other factors that possibly contribute to the prognosis are e.g., the status of the p53 tumor suppressor protein that regulates cell cycle arrest and apoptosis (activated by CBD but also by THC), 1p19q deletions that predict a better survival after both chemotherapy and radiotherapy, or the transcriptional regulator ATRX (mutations are a risk factor for cancer) [8]. Furthermore, mutations of the epidermal growth factor receptor (EGFR) can enhance the division rate of cancer cells, and are a striking characteristic of more aggressive GBMs.

Patients and Methods

Two years ago, we have reported the extension of overall survival in an unselected group of 15 consecutive patients with GBM [9]. All patients received pure phyto-cannabidiol (CBD, >99.8% pure, Trigal Pharma GmbH, Vienna, Austria) in addition to standard treatment; two patients received dronabinol (7.5mg THC/day) in addition to CBD, one of them for eight weeks only (patient number 14), the other patient continued the combined treatment with CBD and THC until death (patient number 5). For further details we refer to our previous publication. At present, three patients are still alive. One subject has been lost to follow up after being alive for 66 months; all others have been followed until death. In the following, we review the characteristics of these 15 GBM patients with the aim to analyse factors favouring their survival. A tabulated summary of these patients together with their age at diagnose, survival time, prognostic molecular factors and the dosage of CBD is presented in (Table 1).

Table 1: Survival time (months) of patients, daily dose of CBD and prognostic factors.

Patient Number°	Age at Diagnose (years)	Survival since Diagnose (months)	Genetic Markups	Dose of CBD (mg / day)
11	31	66 (* ?)	MGMT, IDH, ATRX,	560
5	61	64	MGMT, 1p19q,	400+
6	41	60*	MGMT,	400
1	40	51	n.d.	400
3	51	49*	MGMT, *IDH*,	600
15	65	40*	MGMT, *IDH*, ATRX,	400
14	56	37	MGMT,	400+
7	76	28 (median)	n.d.	500
2	57	21	n.d.	400
10	54	14	*MGMT*, *IDH*,	600
13	35	14	n.d.	200
4	60	13	*IDH*, ATRX, p53, *EGFR*,	200
12	49	13	*IDH*, ATRX,	400
9	68	8	MGMT, *IDH*, *1p19q*,	200
8	66	7	*IDH*, ATRX, p53,	200
Sum 15		Mean 30.9 months		

Genetic markups: favourable prognostic factors are, e.g.: MGMT methylated, IDH mutated, ATRX preserved or p53 preserved, or 1p19 deleted; unfavourable factors are in *italics* (e.g., unmethylated / unmutated markers); n.d.: no data;

[+] - patient received also THC (7.5mg/day) in addition to CBD; * still alive;

° numbers refer to the same patients as in the publication of Likar *et al.*, (2021) [9].

Results

Of 15 patients, 8 (53%) survived for more than 2 years, 7 (47%) for more than 3, and 3 patients (20%) at least for 5 years. Of these three patients, one is still alive, another died after 5 years, and one patient has been lost to follow-up after 66 months (patient number 11). Currently, three patients are still followed (patient number 6, 3 and 15, alive since 60, 40 and 49 months respectively). The median survival time is 28 months, the mean survival is actually 30.9 months.

The median divides patients in two equally sized groups, those with a shorter or longer overall survival respectively. As can be seen, there is no striking difference between the groups in terms of age at diagnose or prognostic molecular factors. However, in the group of patients with a survival time lower than the median, four patients had received only

200mg CBD per day whereas those surviving longer than 28 months had all been treated with 400 to 600mg CBD/day. This suggests that a higher dose of concomitant CBD is more effective, and supports the assumption that CBD contributes to the extension of the overall survival of patients with GBM.

Discussion

The exact mechanism behind CBD's tumor suppressing effect is complex and still incompletely understood. CBD targets tumor cells by multiple mechanisms; it increases endocannabinoid levels particularly of anandamide (AEA) by targeting fatty acid amid hydrolase (FAAH), upregulates the production of reactive oxygen species (ROS) which are toxic to tumor cells, exhibits anti-inflammatory properties via the peroxisome proliferator-activated receptor gamma (PPARγ), and inhibits the GPR55 receptor while activating TRPV1 among many other targets. CBD enhanced also p53-mediated induction of apoptosis [8]. In combination with TMZ, the activity against GBM cell lines was improved *in vitro*, and the survival of tumor-bearing mice was prolonged, possibly via inhibition of the expression of RAD51, a DNA repair protein in MGMT-metylated tumors [10]. Moreover, CBD is able to modify DNA methylation in the brain by regulating the activity of the respective enzymes [11-13].

Conclusion

The main limitation of this case series is that GBM patients are only compared to historic controls. However, overall survival is generally considered as a "hard" and objective endpoint that make results less sensitive to host- or environment-related influences. Results suggest that CBD, in a daily dose of 400mg or higher, in combination with standard treatment, results in a more effective inhibition of GBM-progression, and - in the average - in a three to five times longer survival.

Conflicts of Interest

None.

Author Contributions

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

Ethical Statement of Informed Consent

The local Ethics Committee has consented to the treatment with cannabinoids; informed consent for participation was obtained from the patients.

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