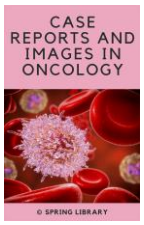

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Research Article

Report of Objective Responses of Prostate Cancer Patients to Pharmaceutical Grade Synthetic Cannabidiol

Julian Kenyon[1*], Andrew Davies[2] and Colin Stott[2]

[1]*The Dove Clinic for Integrated Medicine, UK*
[2]*Alinova Biosciences, UK*

ARTICLE INFO

Article history:
Received: 18 August, 2020
Accepted: 7 September, 2020
Published: 21 September, 2020

Keywords:
pharmaceutical grade synthetic cannabidiol, prostate cancer

ABSTRACT

This is an observational study of objective responses of Prostate Cancer patients to Pharmaceutical Grade Synthetic Cannabidiol. The total number of patients in the study was 12, 11 had a response of one kind or another.

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1. Introduction

The use of a whole variety of cannabis oils of questionable quality, none of which were pharmaceutical grade, and all bought on the internet has been a matter of routine by cancer patients, especially prostate cancer patients. No anticancer effect of these oils has been noted [1-3]. Currently, it is illegal to buy cannabis oil on the internet as the Medicines and Health Regulatory Agency has defined CBD as a medicinal product, which can only be prescribed under the Pharmaceutical Specials scheme, as it is not currently a licensed medicinal product [4]. Cannabidiol targets CB1 and CB2 receptors, which have increased expression in prostate cancer as compared to normal prostatic tissue [5], and the overexpression of CB1 receptors has been associated with a higher Gleason Score and metastasis incidence, being a negative marker of disease outcome [6, 7]. Cannabidiol targets CB1 and CB2 cannabinoid receptors.

The phytocannabinoids are a group of chemicals extracted from the cannabis plant. A number of them are able to impede cancer cell growth, induce apoptosis and autophagy, and inhibit angiogenesis. The most widely known phytocannabinoid is Δ9-tetrahydrocannabinol (THC), and although it possesses these anticancer effects, it is also psychoactive, which has arguably hampered its clinical development. It is thought that these actions are mediated, in part, by binding to cannabinoid receptors that are expressed on a number of tissue types [8]. As one type of the receptor is found exclusively on brain cells, studies using THC have focused on this tissue type. *In vitro* data were promising, and in 2016, a pilot clinical study in patients with glioblastoma multiforme indicated THC was safe; however, no clear activity was reported [9]. The dosages were possibly on the conservative side, to minimise psychoactivity that would naturally restrict the use of THC as drug.

Of the 80+ phytocannabinoids, THC is possibly the only one to exhibit this psychoactivity. More recently, studies have diverted away from THC and focussed on other cannabinoids. The next most abundant compound is cannabidiol (CBD), which has a low affinity for the canonical cannabinoid receptors. In contrast to THC, in its pure state, according to the World Health Organisation, CBD did not have abuse potential and caused no harm [10]. Studies have shown that in addition to being able to induce cell death directly, it is also capable of interfering with intracellular signalling [11]. Alterations to pathways such as the PI3K/AKT/mTOR and the ERK suggests that CBD can modify the way certain cancer cells react to other treatments.

Indeed, studies have shown that combining CBD with conventional chemotherapy such as cytarabine and vincristine can lead to enhanced anticancer activity through modifications to these signalling pathways [12, 13]. Furthermore, the sequence in which these drugs are administered can also influence overall activity. Studies have also indicated that in certain leukaemia cell lines, CBD can increase the expression of the cyclin-dependent kinase inhibitor p21[13]. This increased level appears to be maintained by CBD, which inadvertently impedes cell death. Cytotoxicity could be restored in these cells if the

[*]*Correspondence to: Dr. Julian Kenyon, The Dove Clinic for Integrated Medicine, UK; E-mail: jnkenyon@doveclinic.com*

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http://dx.doi.org/10.47496/nl.CRIO.2020.01.06

treatment regimen was altered to allow for a temporary cessation of exposure to CBD. Thus, the general efficacy of CBD may also be altered by adapting treatment protocols that include "drug-free" phases [13].

The findings from a number of studies designed to examine the role of cannabinoids in the management of cancer symptoms varied [14]. The most recent prospective analysis of nearly 3,000 patients using medical marijuana showed that a large proportion of patients reported improvement in their condition [15]. Patients often feel that conventional therapies are not working for them, and so they search the internet for alternative medicines. It is here that they find stories about cannabis working in patients with cancer, and understandably feel it is a route for them. The cannabis products they use vary and can be in the form of whole-plant extracts or purified oils; however, whatever the source, they self-prescribe dosages. A number of anecdotal positive responses have been reported, which sustains the interest in this type of medication.

We have previously reported on objective clinical responses in a variety of cancer patients using pharmaceutical grade synthetic cannabidiol (PGSC) [16]. Over five years ago, we decided to assess the potential use of PGSC in prostate cancer patients. Some of the cases reported here were presented in our previous paper [16].

2. Materials and Methods

Patients were given PGSC (STI Pharmaceuticals), under the Pharmaceutical Specials scheme in oily drops at 5% (w/v) in 20ml bottles. Each drop contains 1mg of synthetic CBD in neutral oil. This was prescribed on an informed consent basis. Of the 12 patients described here in this observational study, every patient in this study signed an informed consent allowing anonymous use of their data. The medicinal use of synthetic cannabinoids has been extensively reviewed in a recent paper [17]. CBD was administered on a three days on and three days off basis, which clinically is found to be more effective than giving it as a continuous dose. The average dose was 10mg twice a day. For increased tumor mass, the dose was increased, in some cases up to 30 drops (30mg). We clearly demonstrated that there is a dose-response relationship in the treatment of cancer using PGSC.

In a number of cases where there was stable disease, the dose was reduced to 5 drops (5mg) twice a day. In one case in this study, Sativex, which is licensed for use in multiple sclerosis, was used in conjunction with CBD as a source of THC, which synergises with CBD [18]. A fraction of the dose used for multiple sclerosis was used. Two sprays of Sativex were given twice a day on a three days on and three days off pattern, as in the case of the PGSC. Patients on continuous dosing did not do as well as those on an on/off repeating regimen. We assessed the majority of patients using circulating tumor cells tests [19, 20]; some decided not to have this.

3. Results

The results of our prostate cancer cohort previously treated with PGSC is reported here in significantly more detail than in our previously published study [16]. This has been in response to many requests for more details on outcomes. The results are shown in (Tables 1 & 2). We were unable to define a maximum tolerated dose of CBD, as there was an absence of significant side effects. The only noted side effects were some degree of drowsiness in those patients who received a dose of 20mg twice a day or above. This side effect did not persist. All cases showed a response either in circulating tumor cells [19, 20], in those who had this test done or in reducing PSA levels. All of those who stopped taking PGSC showed a subsequent increase in circulating tumor cells or in PSA. In patient P12, with a break in the supply of the PGSC, the circulating tumor cells went up from 1.2 cells per 7.5ml to 2.0 cells per 7.5ml, over a six-month period [19].

TABLE 1: Outcomes-prostate cancer.

Tumour Free	1
Stable Disease	10
Circulating Tumour Cell Tests	6
Extended Median Survival	1
Died	1
No Effect	1
CBD Only	9
Bicalutamide	2
Prostatectomy	1
Radiotherapy	1
Unknown Outcome	1
Total Cases	12

TABLE 2: A detailed list of all of the patients in this observational study.

Age	Diagnosis	Standard Treatments	CBD only treatment?	Circulating Tumour CellsTest	
M 59 (P1)	Gleason 7 Prostate Cancer	Prostatectomy	✓	Sept 2018 2.4/7.5ml Sept 2019 1.4/7.5ml	Diagnosed in 2017. His PSA has remained on average 0.01.
M 79 P(2)	Gleason 8 Prostate Cancer	None (Bicalutamide)	×	Not done	Diagnosed 2003/ We started him on PGSC in February 2018. He was also on Bicalutamide. No significant effect on his PSA, which was the only test he had done, was detected, presumably because he was on Bicalutamide.
M 82 (P3)	Metastatic Gleason 7 Prostate Cancer	None (Bicalutamide)	×	Not done	Diagnosed in 2012. He was put on Bicalutamide but became hormone resistant by January 2017. In April 2017 we put him on PGSC 20 drops twice a day, three days on

					and three days off. His PSA on starting PGSC was 15, this dropped to 7.3 in April 2018. His expected survival when we saw him in January 2017 was six months, actual survival was 15 months.
M 70 (P4)	Gleason 7 Prostate Cancer	None	✓	January 2019 8.5/7.5ml July 2019 3.2/7.5ml	Diagnosed in June 2018. PSA was 11.9. His PSA in January 2019 was 4.3. We put him on PGSC in June 2018 and this was the only treatment. His PSA has remained on average 4.3 throughout this time.
M 81 (P5)	Gleason 7 Prostate Cancer	None	✓	Not done	Diagnosed in 2013. Initial PSA when we saw him in June 2015 was 3.8. We put him on PGSC in June 2015. By June 2016 his PSA had dropped to 1.3. In 2017 he stopped the PGSC. In December 2017 the PSA had risen to 2.4 and it rose again to 3.6 in June 2018.
M 82 (P6)	Gleason 7 Prostate Cancer				This patient has been lost to follow up.
M 75 (P7)	Gleason 7 Prostate Cancer	None	✓		Diagnosed in October 2015. His PSA was 7.6 at presentation. We put him on PGSC in February 2016, his PSA dropped to 6.6. A year later, his PSA was 6,1 He stopped taking the PGSC at the end of 2017 and in April 2018 his PSA went up to 7.3 and then up again to 8.7 in May 2018.
M 76 (P8)	Gleason 9 Prostate Cancer	Radiotherapy Bicalutamide	×	May 2019 2.1/7.5ml Dec 2019 2.2/7.5ml	Diagnosed August 2018. He has had Radiotherapy and is on Bicalutamide. His Circulating Tumour Cell tests immediately after the Radiotherapy showed zero cells per 7.5ml. We started him on PGSC. His PSA in May 2019 was 0.78, his Circulating Tumour Cells test showed 2.2 cells per 7.5ml.
M 74 (P9)	Gleason 7 Prostate Cancer	None	✓	Oct 2015 4.8/7.5ml July 2016 4.2/7.5ml Nov 2-16 3.2/7.5ml May 2017 3.8/7.5ml Nov 2017 5.9 April 2018 4.6 Oct 2018 3.3 May 2019 3.1	Diagnosed in 2014 He refused all standard treatments. We put him on PGSC in October 2015. His Circulating Tumour Cells were 4.8 at that time. In July 2016, 4.2, November 2016 was 3.2, May 2017 3.8, November 2017 5.9, April 2018 4.6, October 2018 3.3, May 2019 3.1. He has refused to have any PSA tests because he finds them confusing and unreliable. PGSC is his only treatment.
M 83 (P10)	Gleason 8 Prostate Cancer	None	✓	Nov 2014 4.1/7.5ml April 2015 3.7/7.5ml July 2019 2.4/7.5ml	Diagnosed in July 2014. Refused all standard treatments. He has been on PGSC only from January 2015. His Circulating Tumour Cell Test in November 2014 was 4.1 cells.7.5ml. In April 2015 this was 3.7. In July 2019 this was 2.4. His PSA has remained on average 30 since July 2014.
M 84 (P11)	Gleason 7 Prostate Cancer	Bicalutamide	×	Aug. 2017 3.7/7.5ml	Diagnosed in December 2015. On Bicalutamide. Circulating Tumour Cells test carried out in August 2016, 3.7 cells.7.5ml. This test has not been repeated. He had six months of PGSC in 2016. His PSA has remained on average 0.3 since starting on the Bicalutamide in December 2015.

M 71 (P12)	Gleason 8 Prostate Cancer	Bicalutamide	×	Dec 2016 4.7/7.5ml June 2017 2.9/7.5ml April 2018 3.9/7.5ml Aug 2018 2.1/7.5ml Feb 2019 1.2/7.5ml Aug 2019 2.0/7.5m	Diagnosed in December 2016. He had Sono and Photodynamic Therapy [21] in August 2018, he also had Faecal Microbiome Transplantation at the end of 2018 [19]. His PSA has remained at 0.1 throughout the time we have seen him. The last increase in Circulating Tumour Cells test, between February 2019 and august 2019 coincided with us being unable to obtain PGSC for several months. We added in Sativex at the patient's request to his PGSC.

3. Discussion

PGSC is shown in this paper to have significant anticancer effects. This study is an observational study, and prospective randomised control studies are worth doing using this approach, as it is free from side effects. The weakness of this study is that it is an observational study.

4. Conclusion

PGSC has an objective anticancer effect in prostate cancer patients. To elucidate this further, then further studies addressing the weakness of this particular study are worth carrying out. This study was supported by a research grant from Alinova Biosciences.

Conflicts of Interest

None.

Funding

The writing of this study has been made possible by a grant from Alinova Biosciences.

Acknowledgements

Julian Kenyon would like to acknowledge the contributions made by Andrew Davies and Colin Stott to this paper.

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