Towards the utilization of cannabinoids as anti-cancer agents

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Anti-cancer activity of cannabinoids

Munson et al. (1975) Antineoplastic activity of cannabinoids
Cannabinoids exhibit anti-tumor activity in many different animal models of cancer.

- Glioma
- Melanoma
- Skin carcinoma
- Lung cancer
- Breast cancer
- Hepatocellular carcinoma
- Pancreatic adenocarcinoma
- Leukaemia
- Prostate cancer
Antitumoral action of cannabinoids

Selectivity of cannabinoid anticancer action

Potential clinical application
A 1st Pilot Clinical trial (2003-2006)

Glioblastoma (GBM)

GBM diagnosis (n=9)
1st Surgery
Radiotherapy ±Chemotherapy
Relapse
Infusion catheter (Pre-treatment tumour biopsy)
THC treatment
Post-treatment tumour biopsy
Decease

EXPERIMENTAL PERIOD SURVIVAL
**THC activates the autophagy-mediated cell death pathway in human glioblastoma samples**

**Cell proliferation (Ki67)**

- Pre-THC
- Post-THC

**Angiogenesis (CD31)**

- Pre-THC
- Post-THC

**Autophagy (LC3)**

- Pre-THC
- Post-THC

**Apoptosis (caspase 3)**

- Pre-THC
- Post-THC
Survival of patients

Median survival = 24 wk
(95% CI: 15-33)
Similar to other drugs (e.g. TMZ)
Strategies aimed at optimising cannabinoid anticancer activity

1) Increasing our knowledge on the molecular mechanisms involved in cannabinoid anticancer action

2) Identifying the molecular factors associated with cell resistance to cannabinoid anticancer action

3) Designing the most appropriate cannabinoid-based combinational therapies
Antitumoral action of cannabinoids

CBD and other phytocannabinoids

CBD

CB1, CB2 TRPVs
Other receptors?

ROS

Additional mechanisms

? Autophagy

Apoptosis

Cancer cell death
Strategies aimed at optimising cannabinoid anticancer activity

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3) Designing the most appropriate cannabinoid-based combinational therapies
Predictor of resistance to cannabinoid anticancer activity

Primary cultures of human glioma cells

Cell viability (% from Vehicle)

THC 6 μM **

Gene expression levels (a.u.)

ALDH2 IGFBP5 MDK

PDGFRA CSF1 GBP2 UPP1 ID3

ALDH2 IGFBP5 MDK
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3) Designing the most appropriate cannabinoid-based combinational therapies
Cannabinoid-based combinational therapies for GBM patients?
Cannabinoid-based combinational therapies for GBM patients?

Antibodies targeted to growth factors, such as MDK or VEGF

Receptor tyrosine kinase inhibitors

Selective silencing of resistance factors

Classical chemotherapeutic drugs, such as temozolomide

Cannabinoids

CB1 or CB2

Ceramide

ER stress

Inducers of ER stress and autophagy

Inhibitors of the AKT-mTORC1 axis

p8

TRIB3

AKT

mTORC1

Autophagy

Apoptosis

MDK

ALK

EGFR

AREG

ERK
Standard GBM therapy

GBM diagnosis

Surgery Radiotherapy + TMZ?

TMZ

Relapse

2nd line therapies

Decease

NEWLY-DIAGNOSED GBM

RECURRENT GBM

GBM

RT  TMZ/RT

Median OS: 12.1 mos 14.6 mos
2-yr survival: 10% 26%
HR [95% CI]: 0.63 [0.62-0.75]
P<0.0001
Cannabinoids enhance TMZ anticancer activity in GBM preclinical models

U87 MG astrocytoma cells

Similar effect on cannabinoid and TMZ-resistant tumors
Selecting the appropriate cannabinoids for anticancer therapies

- CBD has anticancer activity by itself
- CBD attenuates the psychoactive effects of THC
- Wide experience in the use THC and CBD (Sativex)
Cannabinoids enhance TMZ anticancer activity

**U87 MG astrocytoma cells**

**Peritumoral administration**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean ± S.E.M</th>
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<tbody>
<tr>
<td>VEH</td>
<td>10.3 ± 0.4</td>
</tr>
<tr>
<td>SAT (7.5 mg/kg THC-BDS + 7.5 mg/kg CBD-BDS)</td>
<td>6.2 ± 0.3 **</td>
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<tr>
<td>THC (15 mg/kg)</td>
<td>5.8 ± 0.5 **</td>
</tr>
<tr>
<td>TMZ (5 mg/kg)</td>
<td>4.1 ± 0.4 **</td>
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<tr>
<td>SAT + TMZ</td>
<td>2.6 ± 0.3 ** ΩΩ</td>
</tr>
<tr>
<td>THC (15 mg/kg) + TMZ</td>
<td>2.4 ± 0.3 ** ## ΩΩ</td>
</tr>
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</table>

* ΩΩ: Significant difference compared to VEH
**: Significant difference compared to SAT
##: Significant difference compared to THC (15 mg/kg)
Cannabinoids + temozolomide therapy for GBM patients

Second line study (started)

GBM diagnosis

Surgery Radiotherapy + TMZ?

Relapse

Sativex + TMZ

Decease

NEWLY-DIAGNOSED GBM

RECURRENT GBM

Relapse

Do MK levels predict resistance to Sativex + TMZ therapy?

GBM

diagnosis

Surgery

Radiotherapy

+TMZ?

TMZ

Decease

Recurrence

Do MK levels predict resistance to Sativex + TMZ therapy?
Clinical Trial (ongoing)

**Primary objectives**
- To determine the *safety profile of Sativex® in combination with TMZ*
- To provide preliminary *evidence of anti-tumoural activity* for this drug combination (comparison with a high-dense regime of temozolomide)

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<tr>
<td>1</td>
<td>Active, not</td>
<td><strong>A Safety Study of Sativex in Combination With Dose-intense Temozolomide in Patients With Recurrent Glioblastoma</strong></td>
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<td><strong>Condition:</strong> Cancer</td>
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<td><strong>Intervention:</strong> Drug: Sativex</td>
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<tr>
<td>2</td>
<td>Active, not</td>
<td><strong>A Safety Study of Sativex Compared With Placebo (Both With Dose-intense Temozolomide) in Recurrent Glioblastoma Patients</strong></td>
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Other clinical studies with CBs as anti-cancer agents

A Study: Pure CBD as Single-agent for Solid Tumor.

This study is not yet open for participant recruitment. (see Contacts and Locations)

Verified September 2014 by Hadassah Medical Organization

Sponsor:
Hadassah Medical Organization

Information provided by (Responsible Party):
Rotenberg Yair, Hadassah Medical Organization

Purpose

Increasing lines of evidence support an antitumorigenic effect of cannabinoids, including the cannabidiol (CBD) which does not possess the psychotropic effects of D9-tetrahydrocannabinol (THC). These include anti-proliferative and pro-apoptotic effects and they are known to interfere with several mechanisms in the tumorgenesis. Yet, evidence from clinical trials among cancer patients is needed. The aim of the current study is to evaluate the impact of CBD as single treatment among cancer patients.

A Study of Dexamabinol in Combination With Chemotherapy in Patients With Advanced Tumours

This study is currently recruiting participants. (see Contacts and Locations)

Verified April 2015 by e-Therapeutics PLC

Sponsor:
e-Therapeutics PLC

Information provided by (Responsible Party):
e-Therapeutics PLC

Purpose

This is a trial of dexamabinol in patients with advanced tumours. The purposes of the protocol are to study different doses of the study drug to determine the maximum safe dose of the drug given in combination with standard chemotherapies and to further understand the safety of the study drug and to measure any reduction in size of patients' cancer tumour(s).

Dexamabinol is a synthetic cannabinoid which has previously undergone clinical trials for traumatic brain injury (TBI) and in subjects undergoing coronary artery bypass surgery. Currently dexamabinol is under investigation for potential anti-tumour activity in patients with advanced tumours.
Future clinical studies
Selecting the appropriate cannabinoids for anticancer therapies

THC + CBD (1:1)
Other ratios THC:CBD
CB1/CB2 agonists?
FAAH/MAGL inhibitors?
Other phytocannabinoids?

Optimizing delivery methods/via of administration

Marijuana (THC/CBD)
Sativex
Marinol (THC)
Cesamet (Nabilone)
Which cancer types?

Cancer types lacking effective treatments

Glioma

Melanoma

Pancreatic adenocarcinoma
Which cancer types?

Subtypes of cancer that do not respond to current therapies

- Breast cancer
- Prostate cancer
**Combinational therapies?**

- CBs + Classic anticancer treatments (ChT and RT)
- CBs + Targeted therapies
- CBs + Classic anticancer treatments (ChT and RT) + Targeted therapies

Additional preclinical research is still required
It is essential to identify the molecular factors associated with the resistance/sensitivity to cannabinoid anticancer action in clinical studies.