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Case Series

# Cannabidiol Possibly Improves Survival of Patients with Pancreatic Cancer: A Case Series

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ABSTRACT

**Background:** Pancreatic cancer ranks among the deadliest solid tumors. When patients complain about symptoms, the tumor has already spread in the majority of cases to neighbouring tissues and organs with limited possibilities for surgical interventions. In a very recent population-based study which included a total of 36,453 patients with pancreatic ductal adenocarcinoma, median overall survival was only 3.8 months. A growing number of articles suggest potential anticancer benefits of cannabinoids, in particular of cannabidiol (CBD). This is the first time that treatment experiences with CBD are described in patients with pancreatic cancer.

**Case Series:** A total of nine consecutive patients with pancreatic cancer received CBD. All but two received standard chemotherapy in addition, two patients only CBD. CBD was usually administered in an oral daily dose of 400mg. The mean overall survival of these nine patients was 11.5 months (median 11 months).

**Conclusion:** Overall survival seems to be about two times longer than reported in the population-based study mentioned above.



## Introduction

Pancreatic cancer is on the rise; it has been predicted that by the year 2017 in the EU more deaths from pancreatic cancer will occur than breast cancer [1]. Pancreatic cancer is one of the deadliest solid tumors with pancreatic ductal adenocarcinoma (PDAC) being the most common form (about 90%), and with the worst prognosis [2]. Ductal adenocarcinoma is preferentially localized to the head of the organ (75%), followed by the body (15-20%) and tail (5-10%) [3]. Pancreatic cancer is rarely diagnosed in time; in 2/3 of the cases, the tumor has already infiltrated adjacent tissues, blood vessels and organs or has formed metastases when patients present with first symptoms. Survival is slightly longer in patients with localised disease, having no metastases, and who received chemo (radio) therapy without resection; resection improves survival further. Optimal treatment typically involves a multimodality approach with surgical resection whenever possible, combined with chemotherapy and radiation. Nonetheless prognosis continues to be generally poor.

In many carcinomas, including pancreas ductal adenocarcinoma (PDAC), the endocannabinoid system seems to be disturbed. Whereas in normal pancreatic tissue cannabinoid receptors CB1 and CB2 are expressed at almost undectable levels, a very high expression of CB1 and low levels of the endocannabinoid degrading enzymes fatty acid amid hydrolase (FAAH) and monoacylglycerol lipase (MAGL) are observed in cancer cells. This disbalance correlates with a shorter survival [4]. Other targets that have been found to be differently expressed compared to normal pancreatic tissue are the orphan cannabinoid receptor GPR55, and the ion channel TRPM8. Both are upregulated in human pancreas adenocarcinoma tissues which correlates with lower overall survival; importantly, CBD acts on both as inhibitor

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[5, 6]. Pharmacologic inhibition of GPR55 by CBD reduces growth, cell cycle progression, and activation of mitogen-activated protein kinase (MAPK) signalling in pancreatic ductal adenocarcinoma cells, whereas the inhibition of TRPM8 reduces proliferation [5, 7]. Other targets that may play a role in pancreatic cancer are TRPM7, the so called "capsaicin-receptor" TRPV1, and TRPV2; both are activated by CBD which induces pro-apoptotic effects [8-10]. Increased expression of TRPM7 (which regulates tumor cell migration) correlates with poor patient prognosis.

Cannabinoids, including cannabidiol (CBD), have been repeatedly reported to reduce tumor cell growth *in vitro* and *in vivo*. In a recent animal study, which used a clinically relevant pancreatic cancer model, CBD improved survival outcomes significantly, and in a similar order as gemcitabine. Even more important, when CBD and gemcitabine were combined, survival was 2.8 times longer than that of controls, and about twice as long with either drug alone [5]. In view of repeatedly described anticancer activities of CBD, and given that CBD is well tolerated, CBD (phyto-cannabidiol, purity at least 99.8%, source: Trigal Pharma GmbH, Wien, Austria) was added as comedication to our patients with pancreatic adenocarcinoma [11-13]. Magisterial CBD capsules or liquids (20% CBD) have been prepared by a local pharmacy. Below we summarise our observations on 9 consecutive cases. The majority of these patients had been seen at other hospitals before presenting in our department.

**Case Presentation**

**Case 1**

Female patient diagnosed at 70 years of age. In November 2017, the patient was hospitalised for nausea and vomiting; a gastroenteritis and colitis were diagnosed, and the patient had been dismissed. In January 2018 the patient complained of thoracolumbar pain; ultrasonography showed multiple hypodense foci in pancreas, liver, stomach, kidney, adrenal gland and peritoneum. A biopsy revealed a ductal adenocarcinoma of the pancreas. Chemotherapy with gemzar-abraxane (gemcitabine and paclitaxel attached to human albumin) was started (total of three courses), in parallel with low dose CBD (100 mg/day). The patient passed away 16 weeks after diagnosis and 14 weeks after start of CBD.

**Case 2**

Male patient diagnosed at 47 years of age. In April 2018 the patient presented with a sudden pain in the upper abdomen radiating to the back, early fullness after meals, and an uncomfortable swelling in the abdomen. Ultrasonography and CT showed an unresectable 3x3 cm mass in the head of the pancreas with multiple round lesions in the liver and enlarged lymph nodes paravertebral, but no ascites and no lung or bone metastases. A CT-guided biopsy demonstrated the presence of an adenocarcinoma. Chemotherapy with gemzar-abraxane was recommended but denied by the patient. Medication with 2x200 mg CBD/day and low dose delta-9-tetrahydrocannabinol (3x2.5 mg THC/day) was started and continued until the patient passed away 15 months after diagnosis, and 14.5 months after starting the treatment with cannabinoids.

**Case 3**

Male patient diagnosed at 47 years of age. The patient had a positive family history as his mother had died from a pancreas carcinoma. The patient suffered from diabetes type II since 2011 and from an adenocarcinoma of the prostate with prostatectomy performed in May 2016 (pT3a, pN1 (1/8), R0; Gleason score 5+3=8) with positive lymph nodes. A PET-CT in June 2016 showed a suspicious lesion (2.9x1.4 cm) on the right adrenal gland. A control (abdominal CT) in September 2016 did not demonstrate any changes. An MRT end of September 2016 however demonstrated an increase of the lesion on the right adrenal gland to 3.6x2.3cm; the lesion was negative in a PSMA-PET examination therefore unlikely of prostate origin. End of November 2016, increased levels of bilirubin and gGT were observed. A cholangiography, PET-CT and MRT were performed and demonstrated a large mass of 4.2x3.2 cm in the head of the pancreas compressing the common hepatic duct as well as increased lymph nodes; a stent was placed in the ductus hepaticus communis.

A pancreas carcinoma was suspected although a biopsy was inconclusive. In December, a 15 mm lymph node near the aorta was excised which did not show malignancy. CBD was started in January 2017 (2x100 mg/day, increased to 2x 200 mg after 3 weeks). A PET-CT in March 2017 showed progressive disease in the head of the pancreas and enlarged para-aortal lymph nodes. In April 2017 an explorative excision of the head of the pancreas was performed and an adenocarcinoma of the pancreato-biliary type was diagnosed (positive for CK7, CK19, negative for CK20, CDX2) as well as metastases in the liver and a peritoneal carcinosis. In June 2017 chemotherapy with gemzar-abraxane was started but stopped after the second course as the patient did not want further chemotherapy. CBD was stopped as well, 13 weeks after the first administration. The patient passed away in September 2017, 11 months after the detection of a suspicious lesion in the pancreas.

**Case 4**

Female patient diagnosed at 67 years of age. The patient had a history of breast cancer operated on in 1997 and subsequent radio chemotherapy. A second surgical intervention was performed in 2009 followed by three courses of fluorouracil, epirubicin and cyclophosphamide, as well as three courses of taxotere. Beginning in August 2016, radiological examinations (MRT, PET-CT) demonstrated a lesion in the head of the pancreas, suspicious for a carcinoma but unresectable, with no enlarged lymph nodes. An explorative laparoscopy and cholecystectomy (histology negative) in August 2016 confirmed inoperability. In September 2016, an Endoscopic Retrograde Cholangiopancreatography (ERCP) was performed, and a stent was placed in the ductus hepaticus communis.

Chemotherapy with gemzar-abraxane was started in September, including also concomitant THC to improve appetite (3x2.5 mg/day). Both were stopped one month later. A MRT control in February 2017 revealed an increase of the tumor in the head of the pancreas, and in the processus uncinatus as well as metastases in the lung, diaphragm and ascites; CBD (2x200 mg/day) was started mid of March and maintained

until the patient passed away mid of April 2017, 8 months after diagnosis.

**Case 5**

Male patient diagnosed at 70 years of age. The patient had a history of COPD, hypertension and hyperuricaemia. In March 2017, a routine laboratory control showed increased bilirubin and a very high level of CA 19-9 (74,800 U/L). In the following, an unresectable, very advanced adenocarcinoma of the pancreas was diagnosed with multiple metastases in the liver. CBD (2x100 mg/day) and monotherapy with gemcitabine was started but stopped after 2 weeks because of fresh ischaemic lesions in the brain. CBD was maintained until the patient passed away 8 weeks after diagnosis.

**Case 6**

Female patient diagnosed at 68 years of age. The patient had suffered since more than two months of increasing, pronounced dyspnoea before admission to the hospital in January 2015. A CT of the lung showed multiple, small, round lesions in both lungs and a suspicious lesion in the pancreas. In addition, increased levels of CEA and CA 19-9 were found. A biopsy of the pancreas demonstrated the presence of an invasively growing, unresectable adenocarcinoma in the body of the pancreas. The resection of one lesion in the lung confirmed metastasis of the pancreas adenocarcinoma. In the following, the patient was lost of sights for 2 years. According to the patient she received during this time one course of chemotherapy abroad (no details available) but had refused further treatments. In January 2017, radiological assessments demonstrated metastases in almost all vertebrae as well as metastases in muscles. In March 2017 the lesion of the pancreas had increased to 6x4 cm, and secondary lesions were found in muscles (greatest lesion 5x2x4 cm). A metastatic lesion with expansion of the thoracic vertebra #7 received palliative irradiation. Low dose THC (3x1.6 mg/day) was prescribed against kachexia and nausea; in addition, CBD (2x200 mg/day) was started beginning in April 2017 and maintained until the patient passed away 28 months after diagnosis.

**Case 7**

Female patient diagnosed at 53 years of age. Beginning of June 2017 an invasively growing, unresectable adenocarcinoma in the body of the pancreas was diagnosed, with multiple metastases in the liver. The patient started the same month with one cycle of chemotherapy with abraxane, followed by one cycle of irinotecan-calcium folinate, 5-fluoruracil (5-FU). CBD (2x200 mg/day) was started in parallel to the chemotherapy mid of June. In July, an increase of the body weight and improvement of pain under comedication with CBD was reported by the patient. A CT in October 2017 showed however progressive disease and further treatment including CBD was stopped. The patient died in January 2018, 7 months after diagnosis.

**Case 8**

Male patient diagnosed at 45 years of age. The patient had a more than 10-years long history of muscular-skeletal pain caused by tendopathia, multiple luxations of both shoulder-joints, lesion of the labrum and use of a number of analgesics. End of January 2017 he complained of abdominal pain, fatigue, loss of appetite and loss of weight and was hospitalised. Examinations with ultrasound and CT demonstrated multiple round lesions in the liver, up to a diameter of 1.9 cm, an unresectable lesion with a diameter of 3.5 cm in the tail of the pancreas and lesions in the spleen. Treatment with CBD (2x200 mg/day) was started in March and increased in April to 2x300 mg and further to 2x400 mg/day. In May 2017, low dose THC (3x2.5 mg/day) was added to his regimen for one month in order to improve his appetite and mood. From June 2017 onwards he received 400 mg CBD per day until April 2018. The patient died end of July 2018, 18 months after diagnosis.

**Case 9**

Female patient diagnosed at 50 years of age. The history the patient revealed nicotine abuse, hyperlipidemia, hypertension, antrum-gastritis and coronary heart disease (with two arterial coronary bypass grafts in 2011). The patient presented early in August 2016 with abdominal pain and cramps. At first glance a pancreatitis was suspected. A laboratory control showed an elevated level of CA19-9 (232 U/l) and a CT demonstrated a lesion of 3x2.5 cm in the area of the processus uncinatus of the pancreas, and a dammed ductus pancreaticus. Pre-operative examinations suggested an advanced but potentially resectable tumor. In September a partial pancreatoduodenectomy (Kausch-Whipple procedure) was performed (tumor staging: pT3N2R0). Chemotherapy with gemcitabine was started in October 2016 together with low dose THC (3x1.6 mg/day). In February 2017, THC was replaced by CBD (started with 2x100mg, increased to 2x200 mg per day in April 2017). Mid of May 2017 chemotherapy was stopped after 6 cycles of gemcitabine and only best supportive care as well as CBD (2x200 mg/day) was further maintained. The patient passed away end of July 2017, 11.5 months after diagnosis.

**Discussion**

Patients in this case series had been referred to our department relatively late when they had already advanced, metastatic disease; this explains the delay for starting concomitant treatment with CBD in most cases. Despite that, mean overall survival in this case series was still 11.5 months (median 11 months); during roughly half of this period patients received also CBD (mean treatment duration 5.2 months). Four patients received also low dose delta 9-tetrahydrocannabinol (THC) for a limited time to improve appetite. According to a very recent population-based Dutch study which included a total of 36,453 patients with PDAC, median overall survival, defined as the time between date of diagnosis and date of death, was 11 months in patients with localised compared to 5.9 months in patients with metastatic disease. Overall survival for the entire cohort that included extended disease/growth outside of the pancreas as well as patients with unknown tumor stage was even shorter, only 3.8 months in the period of 2013-2016 [14].

Notwithstanding that numerous publications on *in vitro* anticancer effects of cannabinoids exist and very promising effects of cannabinoids, particularly of CBD, have been described in various animal tumor models, clinical studies in cancer patients are still very limited. To the best of our knowledge, this is the first observation on a possible, favourable effect of CBD on the survival of patients with pancreatic

cancer. Although it is not possible to predict an individual outcome, patients in our case series seem to survive about 1.9 times longer (median 11 months) compared to patients with metastatic disease in the Dutch study (5.9 months).

In summary, survival of patients in this case series compares favourably with above mentioned population-based data, particularly when considering that two patients (#2 and #8) did not receive chemo or radiotherapy. Intriguingly, the two patients with the shortest survival (#1 and #5) were those who received less than 400 mg CBD per day. Whether a longer/earlier start of treatment and a higher dose and/or other combinations would improve survival is currently unknown and needs further, systematic studies.

## Statement of Ethics

Treatment with CBD was approved by the local ethics committee; all patients had consented.

## Conflicts of Interest

None.

## Funding

None.

## Author Contributions

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

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