VIEWPOINT

Can Cannabis Cure Cancer?

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Not long ago, discussion was focused on whether cannabis caused cancer. A thorough review by the US National Academies of Sciences, Engineering, and Medicine found moderate evidence of no statistical association between cannabis use and the development of lung and head and neck cancers.[1] Limited evidence of a statistical association was found between cannabis use and the development of nonseminomatous testicular carcinomas without good support for a causative effect. Throughout the past few years, the pendulum has swung to the point where many patients with cancer diagnoses are convinced, mainly by internet testimonials, that cannabis, particularly highly concentrated oils or tinctures of Δ^9-tetrahydrocannabinol (THC) and/or cannabidiol (CBD), may actually cure their cancers. What is the basis of this belief?

The bulk of the currently available evidence of a potential anticancer activity of cannabis comes from preclinical models, ranging from cancer cell lines in culture to genetically engineered mice. Overall, these studies have reported that THC, as well as other cannabinoids (either natural or synthetic), can bind to and activate cannabinoid receptors (type 1 [CB_1] and/or type 2 [CB_2]) located on the surface of cancer cells, thereby modulating intracellular signaling pathways. This, in turn, triggers a wide range of antioncogenic effects, including (1) induction of cancer cell death by apoptosis; (2) blockade of cancer cell proliferation; (3) impairment of tumor angiogenesis; and (4) inhibition of cancer cell migration, invasiveness, and metastasis. Ultimately, these actions can lead to a reduction of tumor growth in the host animal.[2]

A desirable property of antineoplastic therapies is their preferential targeting of malignant cells. Both in vitro and in mice, cannabinoids induce apoptosis of cancer cells with no negative effect on the viability of normal nonmalignant cells. Moreover, in some mouse models, the combined administration of cannabinoids together with standard anticancer drugs or radiation therapy acts synergistically to reduce tumor growth with no overt signs of toxicity in the treated animals.[2] Overall, cannabinoids are efficacious, selective, and safe drugs in experimental cancer models.

Yet, oncologists well know that what is observed in culture or animal models does not always readily translate into clinical benefit. The aforementioned National Academies of Sciences, Engineering, and Medicine report veered from the charge to only include meta-analyses of human studies or, absent that, high-quality clinical trials in the chapter on therapeutics that concluded "no or insufficient evidence" of anticancer activity from evaluation of 1 systematic review of 34 in vitro and animal studies.[1] Isolated case reports in the published literature have suggested activity of cannabis-based therapies in a child with terminal acute lymphoblastic leukemia, and internet photographs abound of brain tumors shrinking in response to cannabis therapies, usually after prior conventional therapies had been deemed failures. In the largest case series published to date and to our knowledge, pharmaceutical-grade synthetic CBD was provided to 119 patients with cancer.[3] CBD was the sole treatment for only 28 of them, but the authors report apparent clinical responses in 92% of the patients with solid tumors, providing detailed information on only 2 with rare brain tumors, hence, low-quality evidence.

To date, the scant number of prospective clinical trials of cannabinoids as anticancer agents has concentrated on patients with glioblastoma, which makes sense as mice clearly show a response in preclinical models. In a pilot phase 1 study, 9 patients with recurrent glioblastoma underwent intracranial THC administration.[4] Although no statistically relevant conclusions could be inferred from such a small cohort, the treatment was safe, and some patients seemed to have responded in terms of reduced tumor growth rate as evaluated by magnetic resonance imaging and decreased markers of malignancy in tumor specimens. A randomized, double-blind, placebo-controlled, phase 2 study of the oromucosal cannabis extract nabiximols (THC/CBD 1:1 ratio), added as an adjunct to dose-intense temozolomide, was conducted in 21 patients with recurrent glioblastoma.[5] This study, published only as an abstract to date, concluded that nabiximols offers some efficacy as an adjunct to chemotherapy as the 1-year survival rate was 83% with nabiximols compared with 56% with placebo (P = .042). The median survival exceeded 550 days with nabiximols vs 369 days in the placebo recipients. Ongoing clinical studies of cannabinoids in glioblastoma include a randomized, double-blind phase 2 trial assessing the effect of 2 medicinal cannabis oils with different THC/CBD ratios (1:1 and 4:1) in 82 patients with recurrent glioblastoma (ACTRN12617001287325) and an open-label phase 2 study evaluating the effect of an oral THC/CBD preparation (1:1 ratio) concurrently with standard chemoradiation in patients with newly diagnosed glioblastoma (NCT03529448).

With the high expression of CB_1 receptors in the central nervous system, it seems intuitive that if cannabis is going to have any effect against cancer, brain tumors may be an optimal target. However, analysis of other human tumors has also shown expression of CB_1 and/or CB_2 receptors in the tissue samples.[2] Sometimes the increased cannabinoid receptor expression is associated with improved outcomes and other times, with poorer prognosis. Perhaps it is time for the molecular testing of tumors in the current era of personalized oncology to consider assaying for CB_1 and CB_2 receptor expression and ideally biomarkers of their activity to generate an informative database of how these factors affect outcome and whether the results may

suggest a potential cannabinoid-based therapeutic intervention.

Cannabis and cannabinoids have significant utility as pharmacologic interventions that can be recommended for the management of many of the symptoms associated with cancer or its treatment, including anorexia, nausea and vomiting, pain, insomnia, and anxiety.[6] Because dronabinol (THC) was licensed and approved in 1986 for the treatment of chemotherapy-induced nausea and vomiting, oncologists may have the longest experience of using a cannabis-derived therapy. Surveys show that oncologists are the most supportive medical subspecialty of the use of cannabis by patients, although most confess inadequate knowledge to advise them. There is currently little evidence to suggest that use of cannabis is dangerous in patients with malignant disease although some cautions are offered. For example, CBD is a potent inhibitor of particular cytochrome P450 isoforms, so patients using highly concentrated CBD preparations may risk boosting plasma levels of prescribed pharmaceuticals, thus potentially resulting in increased toxicities. A retrospective Israeli observational analysis suggested that patients using cannabis with immunotherapy had a less robust tumor response to programmed cell death protein 1 inhibitors, although no effect on survival was found.[7]

The suggestion that cannabis may have direct antitumor activity is less embraced by oncologists in view of the absence of evidence from high-quality clinical trials. Providing counsel to patients electing to forego conventional therapy for a curable malignant neoplasm while choosing cannabis as a therapy instead is disturbing. Learning that they might pay up to $7000 per month for their "cure" exacerbates the distress. In the absence of clinical trial evidence, physicians who believe that a patient has successfully been treated for a malignant diagnosis with solely a cannabis preparation should consider that the National Cancer Institute Best Case Series Program evaluates such reports to determine if further investigation is warranted. Unfortunately, many of the patient advocates of cannabis as a cancer cure (on the internet, social media, and in documentaries) forget that they also received conventional cancer therapy, perhaps not an unexpected side effect of their treatment. Despite compelling preclinical evidence, data supporting cannabis-based interventions as effective human anticancer therapies have yet to accumulate with more investigation certainly warranted, although the schedule I designation of cannabis essentially thwarts therapeutic research worldwide.

ARTICLE INFORMATION

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