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Cannabis, Cannabinoids and Cannabis-Based Medicines in Cancer Care

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Abstract

As medical cannabis becomes legal in more states, cancer patients are increasingly interested in the potential utility of the ancient botanical in their treatment regimen. Although eager to discuss cannabis use with their oncologist, patients often find that their provider reports that they do not have adequate information to be helpful. Oncologists, so dependent on evidence-based data to guide their treatment plans, are dismayed by the lack of published literature on the benefits of medical cannabis. This results largely from the significant barriers that have existed to effectively thwart the ability to conduct trials investigating the potential therapeutic efficacy of the plant. This is a narrative review aimed at clinicians, summarizing cannabis phytochemistry, trials in the areas of nausea and vomiting, appetite, pain and anticancer activity, including assessment of case reports of antitumor use, with reflective assessments of the quality and quantity of evidence. Despite preclinical evidence and social media claims, the utility of cannabis, cannabinoids or cannabis-based medicines in the treatment of cancer remains to be convincingly demonstrated. With an acceptable safety profile, cannabis and its congeners may be useful in managing symptoms related to cancer or its treatment. Further clinical trials should be conducted to evaluate whether the preclinical antitumor effects translate into benefit for cancer patients. Oncologists should familiarize themselves with the available database to be able to better advise their patients on the potential uses of this complementary botanical therapy.

Keywords

cannabis, cancer, nausea, pain, antitumor activity, safety concerns, cannabinoids, cannabis-based medicines

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Introduction

At the time the inaugural issue of Integrative Cancer Therapies was published in 2002, 7 states had joined California in making medical cannabis available to patients seeking therapeutic benefit from this versatile botanical. Over the last 2 decades cannabis has been re-installed as a useful substance for medicinal and adult use throughout most of the nation, with medical cannabis available in 37 states and recreational cannabis in 18 states and the District of Columbia. Cancer is an indication for cannabis use in the majority of states that specify eligible medical conditions and oncologists generally support its use in both adults and children with malignant diagnoses.[1,2] As the main psychoactive component of the plant, delta-9-tetrahydrocannabinol (THC) was synthesized, licensed and approved for the treatment of chemotherapy-induced nausea and vomiting in 1986, oncologists theoretically may have the most experience recommending and prescribing a cannabis-based medicine.[3,4] The National Academies of Sciences, Engineering, and Medicine report on the Health Effects of Cannabis and Cannabinoids concluded that some of the strongest evidence for therapeutic benefit was for the use of cannabinoids in treatment of chemotherapy-induced nausea and vomiting.[5,6]

Cannabis, however, still maintains its federal status as a Schedule I substance with high potential for abuse and no accepted medical use. The only legal source of cannabis for clinical research continues to be the National Institute on Drug Abuse despite the wide array of available products that can be obtained at sites selling cannabis in states where it is legal.[7] Sales of cannabis in the United States in 2020 were estimated at $17.5 billion despite still being

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considered illegal by the federal government.[8] Cancer patients are increasingly turning to the use of medical cannabis predominantly for symptom management, most commonly during the phase of active treatment.[9-15] The prevalence of recent cannabis use in patients with a variety of malignant diagnoses ranges from 18% to 40% in surveys conducted in the US, Canada and Israel. With such widespread use of cannabis in cancer patients, it behooves the oncologist to be informed about this widely used complementary botanical therapy.

Cannabis, Cannabinoids, and Cannabis-Based Medicines

The *Cannabis sativa* plant contains over 400 different chemical compounds.[3,5,16] Over 100 of these are 21-carbon terpenophenolic cannabinoids.[17] Delta-9-tetrahydrocannabinol (THC), the main psychoactive component, is found in highest concentration in the resin exuded from the flowers of the female plant. Cannabinol (CBN) is a degradation product of delta-9-THC which is felt to have soporific qualities although available quality evidence is limited.[18] Delta-8-THC was studied years ago in Israeli children receiving chemotherapy and was found to be an effective anti-emetic.[19] In the current era of isolating individual cannabinoids for potential therapeutic benefits, delta-8-THC is emerging as a popular favorite with questionable legal status as it is psychoactive.[20] Cannabidiol (CBD) has catapulted to the top of the most favored cannabinoid list as it is felt not to be psychoactive but to have an array of other therapeutic benefits, although none have been particularly well documented in randomized controlled trials.[21] Purified CBD has been approved as a treatment for children with refractory epilepsy in the form of Epidiolex.[22,23] Cannabigerol (CBG) has also generated a significant amount of interest as a non-psychoactive cannabinoid that is also being touted as a bit of a panacea, absent supporting data from clinical trials.[24]

In addition to the cannabinoids, the plant also contains terpenoids which contribute to the diverse odors of different strains of cannabis and may also have therapeutic benefits in their own right.[17,25] Numerous flavonoids with potential health effects are also present. Many believe that, as opposed to attempting to isolate and study individual cannabinoids, it is the whole plant and the entourage effect of all of its components that is the most effective therapeutic intervention.[17,25]

Dronabinol and nabilone are delta-9-THC medications that have been licensed and approved for the treatment of chemotherapy-induced nausea and vomiting since 1986.[26,27] Nabiximols is a whole plant extract with a THC:CBD ratio of 1:1 that is licensed and approved in much of the world besides the United States for treatment of spasticity associated with multiple sclerosis.[28]

Cannabinoid Receptors and Endocannabinoids

Two cannabinoid receptors have been identified in the human body- CB1 and CB2.[3,5,16,29] These are 7-transmembrane domain G-protein coupled receptors. They are encoded on separate genes and share less than 50% homology. The CB1 receptor is one of the most densely populated receptors in the human brain. The CB2 receptor was initially detected in macrophages and the marginal zone of the spleen with a high concentration in B lymphocytes and natural killer cells. Activation of the receptors inhibits adenylyl cyclase. The receptors have been identified in all animal species down to sea squirts. Animals have these receptors not because they were meant to use cannabis, but because, like endogenous opioids, endogenous cannabinoid also exist. The 2 endocannabinoids that have been most fully characterized are anandamide and 2-arachidonyl-glycerol (2-Ag). Endocannabinoids are produced on demand from membrane lipids and each is metabolized by a separate enzyme (anandamide by fatty acid amide hydrolase (FAAH) and 2-Ag by monoacylglycerol lipase (MAGL)). It has been suggested that the reason for the existence of the system of endocannabinoids and cannabinoid receptors is to facilitate the modulation of pain.

Therapeutic Use of Cannabis and Cannabinoids in Cancer Symptom Management

Nausea and Vomiting

The National Academies of Sciences, Engineering, and Medicine's publication on the Health Effects of Cannabis and Cannabinoids concluded that some of the strongest clinical evidence supporting a therapeutic benefit was that in adults with chemotherapy-induced nausea and vomiting oral cannabinoids are effective antiemetics.[5,6] Numerous meta-analyses have been conducted on the 20-30 studies conducted in the 1970s and 1980s investigating the delta-9-THC pharmaceuticals dronabinol and nabilone. The earlier analyses concluded that these cannabinoids were more effective than placebo and as effective as the standard antiemetics available at that time.[30,31] A later Cochrane Review that included 23 randomized controlled trials concluded that cannabis-based medicines may also be useful in treating refractory chemotherapy-induced nausea and vomiting.[32] Three more recent analyses of these studies, including a systematic review of systematic reviews, were less enthusiastic in their recommendation citing increased side effects compared to standard therapies, lack of comparison to more current antiemetics in the trials and overall low methodological quality of the published reviews.[33-35]

The American Society of Clinical Oncology convened an Expert Panel that concluded that "evidence remains insufficient for a recommendation regarding medical marijuana for the prevention of nausea and vomiting in patients with cancer receiving chemotherapy or radiation therapy."[36] Where is the evidence that cannabis has antiemetic activity? One reason for the lack of data on the botanical itself is related to the significant barriers to studying the potential therapeutic benefit of cannabis in this country.[5,7] Still classified as a Schedule I substance with high potential for abuse and no accepted medical use, cannabis is only legally sourced for research studies from the National Institute on Drug Abuse (NIDA). NIDA has a congressional mandate to study "substances of abuse" as substances of abuse and not as therapeutic agents. Hence very few clinical trials on the utility of the botanical in chemotherapy-induced nausea and vomiting have been published.[31] In two, cannabis was only made available after THC had failed; hence not likely to be successful. The third compared cannabis to dronabinol in a cross-over study in 20 cancer patients and most had no preference.

A Phase II trial of the whole plant extract nabiximols delivered as an oromucosal spray in 16 patients demonstrated that 4.8 sprays of nabiximols was more effective than placebo in further reducing chemotherapy-induced nausea and vomiting in patients on standard antiemetics.[37] A larger multicenter randomized, placebo-controlled trial of an oral THC:CBD cannabis extract was conducted in 81 cancer patients receiving emetogenic intravenous chemotherapy with persistent nausea and vomiting despite standard antiemetics.[38] Patients self-titrated with capsules containing THC and CBD each at 2.5 mg 3 times daily or identical placebo capsules in a crossover design. They were then allowed to choose which they preferred for a third cycle. The complete response was improved from 14% to 25% with the THC:CBD (RR 1.77; 1.12-2.79, $P = .041$). Despite self-reported moderate-to-severe adverse events being more frequent while receiving THC:CBD (31%) compared to placebo (7%) ($P = .002$), 83% of the participants preferred cannabis to placebo.

Lacking data from controlled clinical trials, anecdotal experience from decades of my practice in the San Francisco Bay Area where cannabis has always been readily accessible strongly supports the potential benefit of the inhaled or ingested plant material as an effective antiemetic. Many cancer patients are dismayed by the constipation associated with the use of 5-HT_3 receptor antagonists and may forego them completely in favor of using cannabis successfully as their antiemetic of choice. My clinical observation was supported by a recent survey of 153 non-cancer patients presenting to the Stanford University outpatient general gastroenterology and motility clinics in Palo Alto, California who were asked to rate the efficacy of 29 antiemetics during visits in 2017 to 2018.[39] Antiemetics were scored on a 0-5 scale and the mean efficacy score was 1.73. Cannabis (2.75), ondansetron (2.64), and promethazine (2.46) all scored significantly higher than the mean.

Data from 866 people using the Releaf App give further support to the benefit of the botanical as an effective treatment for nausea.[40] The ReleafApp patient education and cannabis treatment management tool was created to track patient sessions and real-time cannabis use experiences to optimize the therapeutic effects of cannabis consumption while minimizing negative side effects. Releaf App users enter information on the product they intend to consume, including type of product; when applicable, combustion method; plant subspecies; and THC and CBD potency levels. Participants with diverse unstated diagnoses using botanical cannabis to treat nausea reported an average symptom intensity reduction of −3.85 points on a 0-10 scale 1 hour post-consumption. Flower and concentrates yielded the strongest results, with *Cannabis indica* strains underperforming those labeled as *Cannabis sativa* or hybrids. In sessions using the flower, higher THC and lower CBD were generally associated with greater symptom relief. Although no information is given on participant diagnoses, other reviews have noted the observed benefit of botanical cannabis as a useful antiemetic in cancer patients despite limited data from randomized clinical trials.[41-45]

Appetite

Most who have experienced cannabis are aware of an appetite stimulating effect. A small trial involving 2 groups of 3 adult men in a residential setting sought to further delineate this consequence of cannabis use.[46] In this 13-day residential study, men spent the first part of the day working in their room. During the second part of the day, socialization was allowed. Each participant received 2 cigarettes, containing either cannabis with 2.3% THC or placebo cannabis, with instructions to smoke 1 cigarette while alone in their room and the other while socializing. Smoked cannabis increased caloric intake 40%. The increase was noted during both parts of the day. The increased caloric intake occurred with snacks, not meals, and the calories were mainly derived from sweet solid items, not sweet liquids or savory solids.

The indication for dronabinol was expanded in 1992 to include treatment of anorexia associated with weight loss in patients with the AIDS wasting syndrome.[47] The FDA expanded the indication even though dronabinol only increased appetite and not weight in the placebo-controlled trial. Until 1992, the federal government was providing a handful of patients with orphan diseases a cannister containing 300 cannabis cigarettes a month as they had conditions that were felt to respond to cannabis (despite the fact that the Schedule 1 status suggests no accepted medical use).[48] Concerned that thousands of patients with HIV wasting might qualify as orphan disease status and realizing that

it would be difficult to provide each with 300 cannabis cigarettes monthly, the Compassionate Use Program was terminated in 1992 just as the dronabinol indication was expanded. Patients could be advised that they did not need Compassionate Use cannabis as dronabinol was an approved alternative.

One of the largest controlled trials of dronabinol was a randomized study in 469 adults with advanced cancer and weight loss.[49] The study investigated dronabinol 2.5 mg, the progestational agent megestrol acetate 800 mg, or both. Appetite increased in 49% of those receiving dronabinol, 75% of those receiving megestrol and 66% of those receiving both. A weight gain of greater than 10% was seen in 3% of the cannabis recipients and 11% of those on megestrol. Dronabinol was ineffective in leading to weight gain despite increasing appetite. Nabilone did not fare much better in a randomized placebo-controlled study involving 47 outpatients with non-small cell lung cancer treated for 8 weeks.[50] Although the nabilone group increased carbohydrate and caloric intake, there was no significant difference in weight from the placebo recipients. Significant improvements in pain, insomnia and quality of life parameters were reported. Another recent study investigated oil-based capsules containing 9.5% THC and 0.5% CBD to be taken twice a day for 6 months in patients with anorexia-cachexia and advanced cancer.[51] Of the 17 patients commencing the trial, only 11 remained on the study for more than 2 weeks and 6 completed the 6 months. Clearly this sample size is too small to draw any conclusions although the investigators noted that 3 had gained more than 10% from their baseline weights and the other 3 were stable. The participants in this uncontrolled trial reported increased appetite, improved mood and quality of life, and less pain and fatigue. Many patients, however, reported side effects. Three of the 4 patients receiving 10 mg capsules experienced reactions including fatigue, dizziness, disorientation, anxiety, hallucinations, and altered general functioning. Three of the 13 patients on the reduced 5 mg capsules left the study because of similar side effects. Despite the fact that the reported adverse effects were only grade 1 or 2, they interfered with activities of daily life while present.

The last study included CBD with the higher dose of THC. Is CBD the missing ingredient that may lead to increased appetite and weight gain? In the Netherlands, pharmacies provide cannabis preparations with the following THC:CBD contents: 19%:<1%; 12%:<1%; and 6%:7.5%. Data collected from a self-reported therapeutic satisfaction survey revealed that the high CBD strain was reported to produce less appetite stimulation in addition to less anxiety.[52]

One could conclude since none of these trials investigated the complete botanical, that the absence of the entourage effect could explain the lack of weight gain. However, studies of people who are chronic cannabis users suggest that they are less likely to be obese and suffer from metabolic syndrome than non-users.[53] No studies of cannabis to promote weight gain in cancer patients have been reported likely due to the barriers to conducting research with the botanical. Cannabis, however, with both antiemetic and orexigenic effects, may be a useful therapeutic for cancer patients and should be further explored in future clinical investigations.

Pain

Elevated levels of the CB1 receptor are found in areas of the brain that modulate nociceptive processing.[54] Although they were originally felt to act on the same pathways, opioids and cannabinoids act on different receptors and the analgesic effects of cannabinoids are not blocked by opioid antagonists. In addition, CB1 and CB2 receptor agonists have peripheral, as well as central, analgesic actions. Cannabinoids as well as terpenoids may have anti-inflammatory effects which are also analgesic. As concluded in the National Academies of Sciences, Engineering, and Medicine report, some of the strongest evidence for therapeutic effects of cannabis is in relief of pain.[5] Neuropathic pain, particularly HIV-related painful peripheral neuropathy, has been the most investigated and appears to be quite responsive.[55,56] A small trial of vaporized cannabis in diabetic neuropathy was also positive.[57]

Cannabinoids are not only effective in the treatment of rodent models of chemotherapy-induced peripheral neuropathy, but, in some situations, they also have been shown to abort its development.[58-60] To date, there is only 1 published controlled trial of a cannabis-based medicine in chemotherapy-induced peripheral neuropathy.[61] Sixteen patients were randomized to nabiximols or placebo in a crossover trial. Overall, there was no difference between the groups. A responder analysis, however, noted 5 patients reported a greater than 2-point drop in their pain on a 0-10 scale for a mean of 2.6. The calculated number needed to treat for 1 patient to respond from this small trial was 5, suggesting that further investigation is warranted. Clinicaltrials.gov lists only 2 ongoing trials of cannabis-based medicines in chemotherapy-induced peripheral neuropathy. One is investigating hemp-based CBD in colorectal cancer patients (NCT04398446) and the other is evaluating different strength capsules of THC and CBD in 100 patients with taxane-induced neuropathy (NCT03782402).

Randomized double blind, placebo-controlled prospective clinical trials are challenging in general absent the added complexity of investigating a Schedule 1 botanical. In an effort to generate some data, observational studies are increasingly appearing in the literature. Israeli cancer patients who had received at least 2 cycles of chemotherapy including 5-fluorouracil and oxaliplatin were included in a retrospective analysis of chemotherapy-induced peripheral

neuropathy.[62] Two hundred forty-eight patients had used cannabis during their treatment; 116 prior to initiating oxaliplatin and 132 afterwards. Two hundred sixty-five patients who had received the combination chemotherapy but had no history of cannabis exposure during treatment served as controls. Demographics were comparable between groups. Grade 2-3 peripheral neuropathy developed in 15.3% of the cannabis exposed patients compared to 27.9% of the controls ($P < .001$). The protective effect was more pronounced among those who used cannabis first (75%) compared to those who used it after starting the oxaliplatin (46.2%) ($P < .001$). The median oxaliplatin dose was also highest in the cannabis first group (545 mg/m^2) compared to the oxaliplatin first (340 mg/m^2) and control groups (425 mg/m^2) ($P < .001$). Although of lesser strength than those obtained from a randomized, prospective study, these are findings that warrant attention.

Data on cannabis-based medicines in the treatment of non-neuropathic pain is currently limited to trials investigating nabiximols for this indication. Six randomized controlled trials of nabiximols in 1460 cancer patients were subjected to meta-analysis and systematic review.[63] There was no difference between nabiximols and placebo for the difference in change in average pain scores, a finding which remained when only the 3 Phase III studies were included. The cannabinoids were associated with a higher risk of adverse events than placebo as well.

Opiates are widely used analgesics in cancer patients. A pharmacokinetic interaction study investigated the effect of adding vaporized cannabis in patients maintained on their stable doses of sustained release morphine or sustained release oxycodone.[64] Although no clinically significant effect on the plasma opiate levels were seen after inhaling vaporized 3.5% THC for 3 days, improved analgesia was noted. The small 21-person trial was not powered for pain as an endpoint. Observational studies have also suggested that opiate use may be decreased in patients using cannabis for analgesic effects. For example, an Israeli analysis of 2000 cancer patients obtaining cannabis licenses reported that of the 344 on opiates at baseline, by 6 months 36% had stopped and 10% had decreased their dose.[10] No information is provided, however, to determine whether these changes resulted from the addition of the cannabis to their regimen or to the successful treatment of their painful tumors.

Cannabis as an Anti-Cancer Agent

There is much discussion on social media and in documentary films, mostly inaccurate, that cannabis itself has anti-cancer activity.[65] This has led a minority of patients to shun conventional cancer treatments in favor of using highly concentrated oils of cannabis or isolated cannabinoids in hopes of curing their disease. There is increasing evidence from in vitro studies and animal models that cannabis and cannabinoids may have anti-tumoral activity that has not yet been convincingly translated into benefit in humans.[3,16,43,66-72] One of the earliest reports published in the Journal of the National Cancer Institute was from Virginia Commonwealth University investigators who found that delta-9-THC, delta-8-THC and cannabinol all inhibited Lewis lung adenocarcinoma cells in vitro and in mice.[73] CBD failed to inhibit the cell growth and appeared to enhance it. Since this early report, much of the work investigating the anti-cancer effects of cannabis and cannabinoids has been done in Europe and, increasingly, in Israel. Multiple tumor cell lines have been inhibited in vitro. Cannabinoid administration to nude mice curbs growth of a variety of tumor xenografts including gliomas, lymphoma, melanoma and lung, breast, colorectal, and pancreatic carcinomas.[74] The National Academies of Sciences, Engineering, and Medicine report, however, concluded that there was "No or Insufficient Evidence" that cannabis has any activity against cancer as the committee's charge was to review meta-analysis of clinical trials or high quality individual clinical trials.[5] At the time of the literature review, neither were available in the medical literature. The report did include a meta-analysis of 34 preclinical studies in gliomas where all but 1 study showed that cannabinoids selectively kill tumor cells without affecting normal neurons.[75] The anti-cancer effects of cannabinoids in vitro have been elegantly described.[3,16,43,66-75] Cannabinoids have direct tumor killing effects by complexing with the CB1 receptor. This interaction leads to autophagy and increased apoptosis. In addition, cannabinoids have been demonstrated to inhibit vascular endothelial growth factor, thereby impairing angiogenesis and decreasing tumor viability. In vitro studies also reveal that cannabinoids inhibit matrix mettaloproteinase-2 which allows cancer cells to become invasive and metastasize. Hence, pre-clinical evidence suggests that cannabinoids may inhibit tumor growth and proliferation by way of a number of mechanisms.

Despite an ever-increasing body of evidence that cannabinoids may have anti-tumor activity, some pre-clinical findings have been less encouraging. An Israeli team assessed antitumor effects of whole cannabis extracts containing significant amounts of differing phytocannabinoids on different cancer lines from various tumor origins.[76] In the end, they chose 12 extracts to study in 12 cancer cell lines. They reported that specific extracts impaired survival and proliferation and induced apoptosis. The cannabis extracts were more effective than delta-9-THC alone. They found that cannabis extracts could differentially effect cancer cells and cancer cell lines derived from the same organ. Hence, one extract was effective against prostate cancer cell lines whereas another was not. Another investigator assayed expression of CB1 and CB2 in different human tumors.[77] In

some, overexpression of CB1 and/or CB2 was associated with worse prognosis, while in others it was associated with improved survival.

Proponents of the "cannabis cures cancer" movement often site isolated case reports in the medical literature as proof of their claims. On close review issues arise. In one instance, brain tumor patients received conventional therapies in addition to cannabidiol.[78] Spontaneous tumor regression may explain the effect in 2 cases of partially resected pilocytic astrocytomas.[79] Other cases put forth as illustrative do not, in fact, support cancer eradication.[80-82] A recent literature review identified 77 unique case reports describing patients with various cancers using cannabis as a treatment.[83] The data supporting 81% of these cases was considered to be weak. The investigators have established an online, anonymous survey of patients using cannabis for its anticancer effect to assess the impact of the botanical against malignancies (www.catasurvey.com). Preliminary findings suggest that 4 in 10 patients believe cannabis improved control of their cancer.

Two case series have also been put forth as examples of the anti-tumor activity of CBD in particular. Data were collected from 119 patients at a London clinic over a 4-year period who were receiving pharmaceutical grade synthetic CBD oil averaging 10 mg twice a day, 3 days on, 3 days off.[84] Clinical responses were described in 92% of the solid tumor patients, most of whom were also receiving conventional cancer treatments. Only 28 of the patients were receiving CBD alone and no data is presented on their outcomes. Despite the paucity of information presented, the authors suggest that CBD is a candidate for the treatment of breast cancer and brain tumor patients. The second case series describes 9 consecutive brain tumor patients in Vienna receiving pure phyto-CBD at a dose of 400 mg daily in addition to conventional therapy with resection followed by chemoradiation.[85] Six of the patients had glioblastomas and 3 had lower grade tumors. The authors use a historical *median* survival of 14 to 16 months in glioblastoma patients compared to the observed 22.3 months *mean* survival in this cohort to suggest that the CBD was beneficial in this situation. It is not mentioned that the longer survival of the lower grade tumor patients may have skewed the mean value reported and not the use of the cannabinoid.

Clearly with the high concentration of CB1 receptors in the brain, treatment of central nervous system neoplasms with cannabis-based interventions seems a logical place to begin to investigate the potential anti-cancer effects. A study of 9 patients with recurrent glioblastoma was conducted in the Canary Islands.[86] Treatment consisted of 20 to 40 μg of THC delivered via a catheter into the tumor bed for 15 days. The treatment was reportedly well-tolerated, but no difference in survival was noted compared to patients receiving chemotherapy alone. A recently reported Phase 1b trial investigated nabiximols and placebo in European patients with recurrent glioblastoma treated with dose-dense temozolomide.[87] Nine of the 12 nabiximols and 6 of the 9 placebo recipients progressed by 6 months. Despite the similar progression rates, one-year survival was 83% for the nabiximols patients and 44% for the placebo group ($P = .042$), although the investigators state that the small early-phase study was not powered for a survival endpoint. Nonetheless, the trend persisted so that at 2 years 50% of the nabiximols recipients were still alive compared to 22% of the placebo group ($P = .134$). A larger follow-on study is being launched.

An Australian tolerability study of a single nightly dose of 2 cannabis oils in patients with high grade gliomas receiving standard therapies was recently reported.[88] Participants received treatment with oil-based whole plant extracts of cannabis with THC:CBD ratios of either 1:1 or 4:1. Of the 88 participants enrolled, 90% had glioblastomas and 10% anaplastic astrocytomas. Sixty-one patients completed the 12-week study. Physical and functional domains of quality of life and sleep were all improved in the THC:CBD 1:1 ratio group compared to the 4:1. Although the primary objective was to assess the tolerability of the 2 ratios, MRIs were completed at baseline and 12 weeks in 53 participants as disease status was a secondary outcome. At 12 weeks, 11% had a reduction in disease, 34% had stable disease, 16% had a T2 flair and slight enhancement, and 10% had progressive disease. No difference in outcomes was seen between the groups.

Oncologists' Concerns About Cannabis use in Cancer Patients

A random survey was sent to 400 US oncologists with a 63% response rate.[1] Eighty percent of the respondents reported that they discuss cannabis with their patients; for 78% these discussions were patient initiated. Two-thirds of the oncologists felt that cannabis was a useful adjuvant for pain and anorexia/cachexia, but only 46% ever recommend it clinically. This may be due to the fact that only 30% responded that they felt sufficiently informed to make recommendations. It also may be a reflection of concerns that oncologists may have regarding the use of cannabis by patients with cancer. The concept of inhaling a combusted botanical is likely to raise a red flag. In fact, the review of the published literature on cancer causation summarized in the National Academies of Sciences, Engineering, and Medicine report concluded that there was moderate evidence of no statistical association between cannabis smoking and the risk of lung or head and neck cancers.[5] Isolated reports suggesting that cannabis smoking increased both of these tobacco-related malignancies have appeared over the years in the medical literature, but the analysis of the total body of published literature failed to support such observations. The report did note that there was limited evidence of

a statistical association between current, frequent or chronic cannabis smoking and non-seminoma testicular cancer. The statistical association does not imply causation, however. It may be similar to the fact that there are increased drowning deaths in months where ice cream is over-consumed. Similar associations between the use of cannabis and risk of cancer were described in a systematic review including studies published after the National Academies of Sciences, Engineering, and Medicine's review was concluded.[89]

Pulmonary aspergillosis is another concern that oncologists may have about cancer patients smoking cannabis. The first such case was reported in the medical literature by a young NIH fellow named Anthony Fauci.[90] Since that time there have been numerous isolated case reports of patients with various malignancies or other immunocompromised states developing aspergillosis presumably secondary to smoking cannabis.[5] A case control series involving 19 HIV patients with positive aspergillus isolated from their bronchoalveolar lavage was reported.[91] The investigators concluded that the positive finding was associated with absolute neutrophil count less than 1000/mm^3, CD4+ lymphocyte count less than 50/mm^3, steroid use and prior Pneumocystis infection; cannabis use was not associated.

THC and CBD may both impact the metabolism of other pharmaceuticals and botanicals by way of cytochrome p450 interactions.[92] To date, very few pharmacokinetic interaction studies have been investigated to evaluate the effects of cannabis or isolated cannabinoids on blood levels of conventional cancer therapies. One study of a cannabis tea found no interaction with levels of irinotecan and docetaxel.[93] As CBD is a potent inhibitor of many isoforms involved in the metabolism on many prescription drugs, there is a theoretical possibility that patients using highly concentrated CBD oils to treat their malignancy may inhibit the metabolism of conventional therapies conceivably leading to increased toxicity.[92,94] With the wide range of CBD doses accessed by patients from dispensaries, many patients use small amounts of the cannabinoid that are unlikely to cause a pharmacokinetic interaction. However, those using higher doses of CBD and/or THC may potentially precipitate a clinically significant interaction. Oncologists should caution patients about this possibility.

An observational study from Israel concluded that concomitant use of cannabis in association with immune checkpoint inhibitors may detract from the clinical effectiveness of the immunotherapy without impacting survival.[95] A more recent prospective observational study from this group yielded a more concerning outcome.[96] The study included 68 patients with metastatic disease beginning immunotherapy who were not using cannabis and 34 who were. Cannabis use was started from 9 months to 2 weeks prior to commencing immunotherapy. Non-small cell lung cancer and melanoma were the most frequent diagnoses. The investigators reported that the patients using cannabis had a median time to tumor progression of 3.4 months compared to 13.1 months in those who were not ($P = .0025$). In addition, the median survival was 6.4 months in those using cannabis and 28.5 months in those who were not ($P = .00094$). That cannabis use could have such a dramatic impact on both disease progression and survival seems astounding. A statistically significant difference between the 2 groups in this non-randomized observational analysis was that 24% of those using cannabis were receiving immunotherapy as first line therapy compared with 46% of those who were not using cannabis ($P = .03$). The fact that the majority of those using cannabis were receiving immunotherapy as a second or third-line intervention could explain some of the divergence in outcomes. The investigators also note that the cannabis users had less immune-related adverse events, perhaps due to an anti-inflammatory effect of the cannabis which may have also dampened the effectiveness of the immunotherapy. The investigators concluded that "cannabis consumption should be carefully considered in patients with advanced malignancies treated with immunotherapy." As randomized placebo-controlled trials investigating this important question would be difficult to conduct, the results of this study should be shared with patients receiving immunotherapy who may be considering cannabis use.

Conclusions

Despite a dearth of published evidence related to barriers to research, botanical cannabis may be a useful adjunct to standard treatment in alleviating side effects of cancer or its treatment, but further research to produce convincing evidence is needed. Although preclinical findings are promising, there is little support in the medical literature to date for anti-tumor activity of cannabis or cannabinoids. As more tumors are assayed for actionable mutations, it may be of benefit to considering routinely assaying specimens for CB1 and CB2 expression to better understand their relationship to disease progression and response to therapy.[97] More research should be done exploring the impact of cannabis-based therapies on malignant tumors. Oncologists' concerns about cannabis use by patients with cancer can mostly be allayed as most controlled trials report predominantly low-grade adverse effects. More pharmacokinetic information on highly concentrated preparations of cannabis or cannabinoids on conventional cancer treatments would be useful. A caution regarding the use of cannabis in patients receiving immunotherapies is prudent. More research and education is always warranted to allow oncologists to better understand how this versatile botanical and its derivative compounds may benefit their cancer patients.

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