



Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer



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ARTICLE INFO

Keywords:

Cancer
Medical cannabis
Pain

ABSTRACT

Background: Cancer is a major public health problem as the leading cause of death. Palliative treatment aimed to alleviate pain and nausea in patients with advanced disease is a cornerstone of oncology. In 2007, the Israeli Ministry of Health began providing approvals for medical cannabis for the palliation of cancer symptoms. The aim of this study is to characterize the epidemiology of cancer patients receiving medical cannabis treatment and describe the safety and efficacy of this therapy.

Methods: We analyzed the data routinely collected as part of the treatment program of 2970 cancer patients treated with medical cannabis between 2015 and 2017.

Results: The average age was 59.5 ± 16.3 years, 54.6% women and 26.7% of the patients reported previous experience with cannabis. The most frequent types of cancer were: breast (20.7%), lung (13.6%), pancreatic (8.1%) and colorectal (7.9%) with 51.2% being at stage 4. The main symptoms requiring therapy were: sleep problems (78.4%), pain (77.7%, median intensity 8/10), weakness (72.7%), nausea (64.6%) and lack of appetite (48.9%). After six months of follow up, 902 patients (24.9%) died and 682 (18.8%) stopped the treatment. Of the remaining, 1211 (60.6%) responded; 95.9% reported an improvement in their condition, 45 patients (3.7%) reported no change and four patients (0.3%) reported deterioration in their medical condition.

Conclusions: Cannabis as a palliative treatment for cancer patients seems to be well tolerated, effective and safe option to help patients cope with the malignancy related symptoms.

1. Introduction

As the leading cause of death, cancer is a major public health problem with estimates of about 12.7 million new cancer cases a year in USA alone [1]. Palliative treatment in cancer patients is aimed mainly to alleviate pain and nausea. Approximately 70%–90% of patients with advanced cancer experience significant pain [2].

Opioids are currently the cornerstone medication for the treatment of cancer pain, with success rates of 80–90% [3,4]. However, some patients experience inadequate pain relief with opioids and standard adjuvant analgesics and/or experience unacceptable side effects [2,5].

Nausea and vomiting, the most common chemotherapy side effects are considered by patients as the most stressful [6]. Up to three-fourths of all cancer patients experience chemotherapy-related emesis [7]. Despite the advances in antiemetic therapy, nausea and vomiting continue to be a burden for patients undergoing treatment for malignancies.

Cannabis has a long history of medicinal and recreational use that can be dated back thousands of years. Cannabinoids, the active compounds of the cannabis plant, have a potential therapeutic effect on the core symptoms of cancer such as pain and nausea [8], so it is not surprising that cancer patients frequently use cannabis to reduce their symptoms [9].

In 2007, Israeli Ministry of Health began providing approvals for medical cannabis, mainly for the palliation of the cancer symptoms. The most frequent indication for cannabis treatment in Israel is cancer, with about 60% of the Israeli patients reporting cancer as an indication for the treatment. There is a lack of knowledge regarding the characteristics of the patients, their use patterns, adverse effects and efficacy profiles of cannabis use among cancer patients. Therefore, the aim of this study is to characterize the epidemiology of cancer patients receiving medical cannabis treatment and describe safety and efficacy of this therapy.

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2. Methods

2.1. Study population and treatment program

There are currently above 30,000 patients approved for medical cannabis use in Israel and 10,000 (~33%) of them receive treatment at Tikun-Olam Ltd. (TO), the largest national medical cannabis provider which serves annually ~3400 new patients. The study was conducted in the central cannabis clinic and included all cancer patients starting treatment between March 2015 and February 2017.

During the routine treatment process, all willing patients undergo an extensive initial evaluation and their health status is periodically assessed by the treating team. At the intake session, the nurse assesses a complete medical history, educates the patient on the main active ingredients in the cannabis plant, the possible side effects, coping strategies, provides practical training of administration, and gives an explanation of the regulatory process. The patient fills out a medical questionnaire, which includes the following domains: demographics, comorbidities including substance abuse history, habits, concomitant medications, and measurements of quality of life. Furthermore, the detailed symptoms check-list is assessed. Following intake, the nurse advises on 1. suitable cannabis strains out of sixteen strains available that differ in $\Delta 9$ -THC/CBD concentration, 2. method of administration, and 3. starting dose and titration protocol. The medical cannabis license specifies two ways of administration: oil and inflorescence (which include flowers, capsules and cigarettes); almost half the patients (44%) have a license for the combination of oil and inflorescence.

At one and six months after treatment initiation patients undergo a telephone interview to assess the changes in symptom intensity, underlying disease condition, side effects and quality of life. If needed, the nurse can recommend an adjustment of dosage, change of strain or consumption method.

2.2. Study outcomes

For safety analysis we have assessed the frequency of the following side effects at one and at six months: **physiological effects** – headaches, dizziness, nausea, vomiting, stomach ache, heart palpitation, drop in blood pressure, drop in sugar, sleepiness, weakness, chills, itching, red/irritated eyes, dry mouth, cough, increased appetite, blurred vision, slurred speech; **cognitive side effects** – restlessness, fear, psycho-active effect, hallucinations, confusion and disorientation, decreased concentration, decreased memory or other. The patients were asked to provide details of the incidence, duration and severity of the reported side effect.

For the efficacy analysis we used the global assessment approach where the patients were asked: “how would you rate the general effect of cannabis on your condition?” At one-month follow-up the response options included the following categories: significant improvement, moderate improvement, serious side effects, no improvement. At six months, the options were: significant improvement, moderate improvement, slight improvement, no change, slight deterioration, moderate deterioration, significant deterioration.

Treatment success at six months (primary efficacy outcome) was further defined as at least moderate or significant improvement in the patient's condition and none of the following: cessation of treatment or serious side effects.

We used the numeric rating scale to assess the pain level on an 11-point scale (0 = no pain, 10 = worst pain imaginable) [10] [11]. Quality of life was assessed on Likert scales ranging from very poor, poor, neither poor nor good, good to very good [12]. We asked the patients to report all their prescribed medications (medications they take regularly) before treatment and again after six months. The medications were sorted by drugs family according to the ATC distribution.

One-year and two-year follow-up was done based on the status of the patients on one year and two years of treatment or the most updated

status of the patient in November 2017.

This study was approved by the IRB at the Soroka University Medical Center, Beer-Sheva, Israel.

2.3. Statistical analysis

Continuous variables with normal distribution were presented as means with standard deviation. Ordinary variables or continuous variables with non-normal distribution were presented as medians with an interquartile range (IQR). Categorical variables were presented as counts and percent of the total.

We used *t*-test for the analysis of the continuous variables with normal distribution. The non-parametric Wilcoxon test was used whenever parametric assumptions could not be satisfied.

We utilized logistic regression for the multivariate analysis of factors associated with treatment success. We have included the following variables into the models based on clinical considerations: age, gender, pain scale, number of chronic medications, hospitalization in the past six months, employment, car use, previous experience with cannabis, cigarette smoking, quality of life at the baseline, and concerns about cannabis treatment as reflected in the intake form.

Results are displayed as odds ratios with 95% confidence interval. *P* value < 0.05 was considered to be statistically significant. All analyses were performed at the Clinical Research Center, Soroka University Medical Center, Beer-Sheva, Israel using IBM SPSS version 22 (SPSS, Chicago, IL).

3. Results

3.1. Patient population

During the study period, 3845 subjects received a cannabis license under the cancer indication. Seventy-nine patients (2.1%) died before starting the treatment, 146 (3.7%) received the license but opted not to receive the treatment, one patient (0.2%) switched to a different cannabis supplier, and 3619 patients (94.1%) initiated the treatment. Out of these 2923 (80.7%) responded to the intake questionnaire (Fig. 1). Most of the patients have a license to purchase 30 (57.0%) or 20 (23.2%) grams per month, while 3.9% patients have a license for 100–150 g per month.

Four hundred and eighty-nine (16.7%) patients reported having concerns over the initiation of cannabis treatment. The most common were: possible side effects (162), possible addiction (67), loss of control (56), lack of knowledge regarding the effects (56), assumed lack of effect (43), cannabis being an illicit drug [25], worsening medical condition (20), developing or worsening mental condition (17).

Table 1 shows demographic characteristics of the patients. The mean age was 59.5 ± 16.3 years, with 1261 (43.1%) patients being older than 65 and 37 (1.3%) younger than 18; 17.4% of the patients were employed, 31.8% retired, 46.9% did not work and 3.9% did not answer the question. During the six-month period before commencing cannabis treatment, 1576 (53.9%) were hospitalized with the median number of hospitalization days of 10 (IQR 5–25).

Appendix A shows the distribution of comorbidities with disease duration: 429 (14.4%) patients suffered from hypertension and 326 (11.0%) patients had diabetes. The median time for cancer diagnosis was 0.5 year (range 0.5–21).

At the baseline 2970 patients reported on average of 11.1 ± 7.5 symptoms. Appendix B shows the prevalence of symptoms with the majority of patients (2329, 78.4%) reported sleep problems, 77.7% reported pain with a median pain intensity of 8/10 (IQR 4–9), weakness and fatigue were reported by 72.7% of the patients.

Cannabis strains used by the patients include four categories: 1) Twelve [12] $\Delta 9$ -THC-rich indica strains (22–28% $\Delta 9$ -THC) without CBD (< 0.5%), consumed by 91.8% of patients. 2) Three sativa strains rich in $\Delta 9$ -THC without CBD, consumed by 60.5% of patients. 3) One strain

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