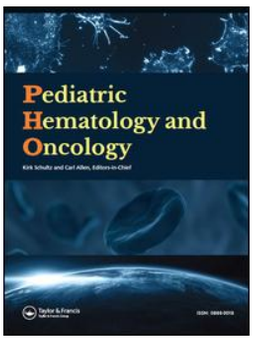

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Medical marijuana use for pediatric oncology patients: single institution experience

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ABSTRACT

Medical marijuana (MM) is widespread in many medical fields, including oncology, with limited use in pediatric oncology where research is scarce and often shows conflicting results. This research focuses on alleviating side effects of anticancer treatment as an integral part of supportive and palliative care of children with cancer. We report our experience with MM treatment in 50 children, adolescents, and young adults with different types of cancer during 2010–2017. The main indications for prescriptions were nausea and vomiting, decreased mood, disturbed sleep, and pain. The medication was supplied to 30 patients via oil drops (60%) and 11 via smoking (22%), followed by vaporization, capsules, or combinations of various routes. Positive effects were reported by verbal children and parents in 80% of cases. MM was generally well tolerated with few patients reporting toxicity, with the most common adverse reactions being burning in the throat and anxiety attacks in subjects who chose to smoke the product. We conclude that MM may serve as a potentially useful complementary therapy to conventional supportive treatment of children suffering from cancer at the end of life. Further research is needed on the safety and efficacy and the consequences of prolonged use in pediatric populations.

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Introduction

Cannabis (marijuana) use has a long history. There is evidence that it was widely used, not only for recreational but also for medical purposes, in such ancient civilizations as Egypt, India, and China. In these countries, the first documented use was more than 5,000 years ago for relief of pain and for anesthesia in various surgical interventions [1]. Currently, there are several countries where medical marijuana (MM) use is relatively widespread and regulated, including Holland, Canada, and Israel.

The Israel Ministry of Health provides cannabis for the following indications: for oncology patients, while giving chemotherapy and until six months from its completion for relieving nausea and vomiting, and pain associated with cancer treatment; for pain relief in metastatic cancer patients after use of all other conventional options; for incurable patients with life-expectancy up to six months. There are other approved uses of

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MM by the Ministry of Health, including chronic nonmalignant pain, inflammatory bowel disease (ulcerative colitis, Crohn's disease) unresponsive to other drug treatments, AIDS accompanied by chronic pain and certain other debilitating symptoms, seizures, and some specific psychiatric disorders.

During recent decades, we have witnessed significant progress in the management of pediatric cancer patients. Survival among children with various types of cancer has reached approximately 80%, with 20% mortality [2]. Mortality is higher than average among children with diagnoses such as brain tumors, metastatic types of bone and soft tissue sarcoma, and high-risk neuroblastoma [3]. The majority of children with incurable malignancies have increasing physical and psychological symptoms as they approach the end of life. [4]. Dealing with the symptoms of physical and psychological distress in this group of patients is frequently very challenging. It is of paramount importance to address this suffering properly and in a successful way in order to assure that quality-of-life in children with cancer during the end-of-life period is maintained at the highest possible level. Pediatric oncologists and pediatric palliative care specialists have various tools at their disposal, both medical and psychological, to optimally control this suffering but, in especially difficult cases, symptoms such as pain, nausea and vomiting, disturbed sleep, and mood changes persist. In these situations, conventional treatment with medications and psychological interventions may be inadequate and other approaches may be of potential benefit. Medical cannabis, also known as labeled MM, may provide an alternative medical solution in such difficult-to-manage situations in pediatric oncology practice.

In the previous decade, there has been an increase in the use of MM among adult oncology patients and, lately, increased interest in using MM to treat pediatric cancer patients. Unfortunately, there is a profound deficit of knowledge on how to use MM in the pediatric oncology population. The literature on this topic is scarce and non-conclusive. There are no data indicating the rational and optimal way of MM dosing and administration, nor have dose finding studies been published in pediatric oncology patients so far. The first license for the use of MM for medical purposes in adults in Israel was given in 1993. Today the State of Israel is one of the world's leading countries in terms of using cannabis and promoting regulations for medical purposes. At the end of 2017, the number of licenses given by the Israel Ministry of Health was nearly 24,000. In Israel, the use of MM in pediatric patients is permitted but there are no data on the numbers of users or results of the efficacy and safety of MM use available to date.

We present our experience using MM for children, adolescents and young adults in the Department of Pediatric Hematology & Oncology. We undertook this study as a descriptive one, looking first of all at what has been parental and sometimes patient experience with the use of MM and what they think about this drug as an additional tool in the management of various aspects of their physical and psychological burden. Our results are the first attempt to analyze efficacy and short-term safety of MM in Israel for this specific subgroup of patients.

Patients and methods

We summarize our experience with prescribing and administrating MM among children, adolescents and young adults from January 2010 to December 2017. During this

8-year period, 798 children, adolescents, and young adults were treated in the Department of Pediatric Hematology & Oncology of the Ruth Rappaport Children's Hospital. Fifty of these children were ultimately prescribed MM for the treatment of their symptoms. The indications for MM prescription were nausea and vomiting, depressed mood, sleep disturbances, poor appetite and weight loss, and pain. Many children were prescribed MM because of a combination of indications listed above. Clinical and demographic characteristics of patients are represented in Table 1 and Figure 1. All patients received comprehensive treatment for the above-mentioned problems without satisfactory success before considering use of MM.

Process of obtaining and starting the use of MM

After having discussed with involved medical and psychosocial staff the medical status of a given patient and arriving at the conclusion that he/she did not have satisfactorily controlled symptoms that are negatively affecting quality of life, we considered the use of MM. First, we offered parents the option of treating their child with medical cannabis. After parental consent was obtained, we involved the children in more discussions

Table 1. Demographic and clinical characteristics of patients.

Demographic and clinical characteristics	N (%)	Median	Range
Age (y)		13.0	7 m–21 y
<5	10 (20)		
>5–12	14 (28)		
13–21	26 (52)		
Gender			
Male	31 (62)		
Female	19 (38)		
Diagnosis			
Leukemia	10 (20)		
Brain tumor	9 (18)		
Sarcoma	21 (42)		
Neuroblastoma	7 (14)		
WT	1 (2)		
Ca	1 (2)		
Lymphoma	1 (2)		
Clinical outcome			
DOD	33 (66)		
Continue with oncological therapy	9 (18)		
Continue after end of oncological therapy	8 (16)		
Initial monthly dose (g)			
20	37 (74)		
30	12 (24)		
40	1 (2)		
Duration of treatment (d)		238	20–1138
0–60	14 (28)		
61–90	5 (10)		
91–180	15 (30)		
>180	16 (32)		
Mode of delivery			
Oil drops	30 (60)		
Smoking	11 (22)		
Oil drops + Smoking	6 (12)		
Capsule	2 (4)		
Smoking + Vaporization	2 (4)		

Notes: WT = Wilms tumor, Ca = carcinoma, DOD = dead of disease.
* One patient with sarcoma did not receive prescribed MM.

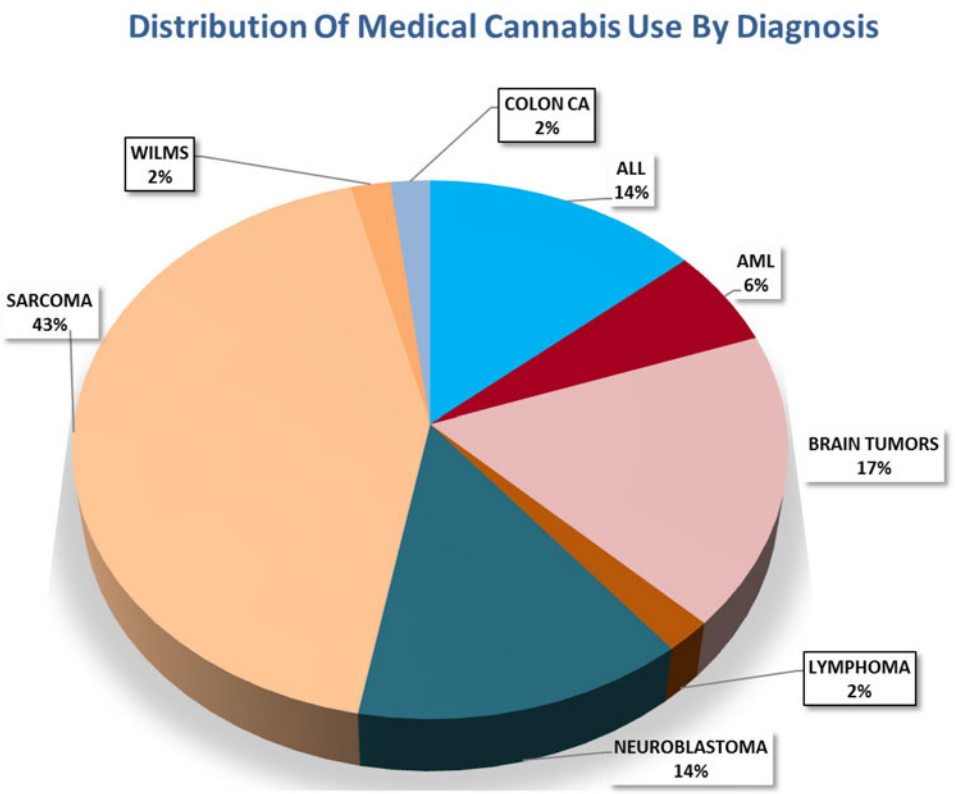

Figure 1. Distribution of patients according to diagnosis.

and explanations and started the process of obtaining a license for providing cannabis. Given the different ways by which MM can be given, we discussed possible pros and cons for each way of administration with the families, thus allowing them to choose the most suitable way for their child. Generally, parents of younger patients preferred oil drops for their children whereas adolescents and young adults more often chose inflorescence for smoking. Followed this discussion, the treating pediatric oncologist completes a special form and sends it to the regional authorized representative of the Ministry of Health for approval and for providing the signed license. After receiving the license, the parents and the child received training on how to use the medicine and instruction about possible side effects. Specifically, the parents were informed orally by the treating physician about possible undesired side effects of MM, such as increased sleepiness, slight decrease in cognitive abilities and concentration and allergic reactions, such as skin rash and wheezing as well as dry mouth and dizziness. It was specifically stressed during the conversation and noted in the written form signed by the parents that, at the present, it is impossible to foresee all possible acute side effect and long-term consequences of MM treatment due to lack of sufficient knowledge.

MM use

Most patients (30, 60%) received MM in the form of oral oil drops, 11 (22%) patients used it by smoking marijuana, six (12%) received MM by combining oil drops and

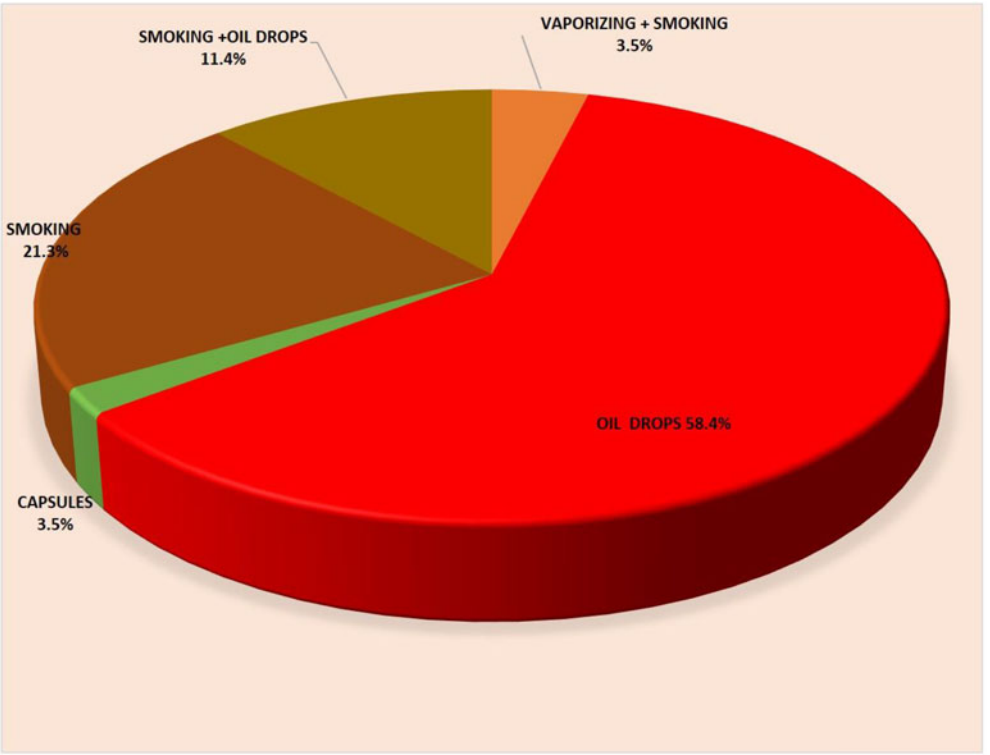

Figure 2. Use of MM according to way of delivery.

smoking, two (4%) patients combined smoking and vaporization, two (4%) received MM in capsules, (Table 1, Figure 2). MM was provided by several producers and distributors licensed by the Ministry of Health. All MM products manufactured in Israel are done so under the auspices of the Ministry of Health and the patients received and used MM with constant and controlled content of delta-9 tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) components. According to Ministry of health recommendations, the starting dose of MM for all patients is 20 grams per month (dry inflorescence cannabis) used for inhalation/smoking or as a basis for oil production. In specific cases a higher dose is possible, with the recommendation and explanation of the treating oncologist. All children, irrespective of patient's age and weight, were given MM orally in the form of oil drops where the concentration of the THC component varied between 0.5% and 1.5% and CBD varied from 3 to 30%. The concentrations of CBD and THC varied more greatly among MM products which were used by patients who preferred smoking (for CBD range was from 0.5 to 19%, for THC range was even wider, varying from 0.5 to 24%). The MM products were introduced to the patients gradually. Thus, the parents and patients were instructed to start with one oil drop orally only for several days at the beginning of treatment with a gradual increase in the number of drops until the desired effect was achieved. Patients who preferred smoking were instructed to smoke MM at the beginning of treatment once daily before the night sleep with a possible increase in the number of MM smoking according to the efficacy of symptoms control.

None of our patients received treatment with any other cannabinoid products (e.g., Dronabinol, Nabilone, Sativex, or Epidiolex) before starting treatment with MM.

MM treatment was commenced either in hospital or at the patient's home, depending on the child's medical condition. All other needed supportive therapy was given concurrently with the MM treatment. Since the use of MM was associated with certain undesired cardiovascular effects such as significant hypotension [5], all patients underwent regular blood pressure measurements as part of routine follow-up and no clinically significant decreases in blood pressure were noted.

Patients reporting outcome

Parents and patients were asked to report on the child's well-being and the effects of the drug, including side effects. We conducted a structured interview with the parents and their child (when deemed appropriate according to the level of cognitive abilities and language mastering of the corresponding children) and asked them about the effects of MM on their symptoms. We asked parents about reincorporation of their children into normal, age-adjusted social life and activities, such as school and communication with peers and friends, and about their overall satisfaction with the MM treatment. The original questionnaire was written in Hebrew; for the families of Arabic origin, the assessment was performed with the help of Arabic-speaking medical personnel. The questionnaire was descriptive and semi-quantitative. It was not validated and was used for assessment of efficacy and safety of MM treatment within our institution only.

We asked parents and patients questions according to the following domains:

1. Pain—type of predominant pain: somatic, neuropathic. Intensity of pain according to Visual Analog Scale (VAS), Numerical Rating Scale (NRS) or FLACC (Faces, Legs, Activity, Cry and Consolability) scales. We also asked if the use of MM had led to a decrease in doses and frequency of use of other analgesics (yes/no).
2. Appetite—increase in appetite (yes/no), weight dynamics during the period of MM use.
3. Sleep—easiness to fall asleep, number of hours of uninterrupted sleep, early awaking.
4. Nausea and vomiting—any changes in intensity and number of N&V episodes per day.
5. Mood—any changes in mood during different parts of the day, including improvement in intra- and interfamily relations (yes/no; if yes, to what extent—minor, moderate, significant).
6. Others—itching, cough, other irking symptoms—yes/no; if yes, to what extent—from minimal to complete disappearance.
7. Side effects—any side effects or unpleasant feelings that parents and/or patient think are caused by MM use.

The assessment was performed at regular intervals during routine visits of patients to our clinic and also at least every three months when renewal of MM use

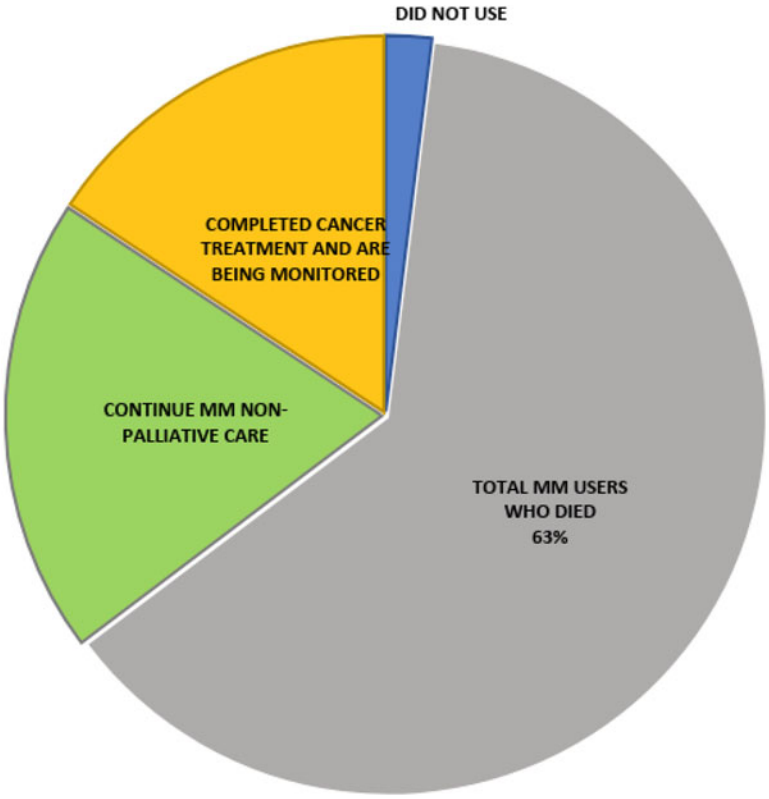

Figure 3. Distribution of patients according to disease status.

permission was needed according to acting regulations established by the Israel Ministry of Health.

Results

Thirty-three (66%) patients who were prescribed MM ultimately died of their diseases. The rest received treatment during anti-cancer therapy, including bone marrow transplantation. Nine (18%) patients continued MM treatment without being regarded as palliative patients (life expectancy less than 6 months) and are currently continuing to receive anti-cancer treatment. Eight (16%) patients continued MM therapy after their anti-cancer treatment was completed, due to prolonged symptoms caused by previous disease or treatments, such as decreased appetite, neuropathic pain, sleep disturbances, etc. (Table 1, Figure 3). Forty (80%) children and parents reported a high level of general satisfaction with the use of cannabis. They told their treating physicians that they thought MM was helpful in alleviating physical and psychological suffering. The experience of patients and parents with the use of MM according to various domains of suffering is shown in Table 2. The duration of MM treatment, as of April 1, 2018, ranged from 20 days to 1,138 days (median, 181 days).

Based on the interviews, children, and adolescents who used medical cannabis and were verbal also reported improved quality of sleep, appetite, and feeling better overall.

Table 2. Tabulated effects of MM administration based on questionnaire responses.

Domain	Positive effect, *N* (%)	Negative effect, *N* (%)	No effect, *N* (%)
Pain	35 (70)	0	15 (30)
Nausea and vomiting	42 (84)	0	8 (16)
Sleep	42 (84)	0	8 (16)
Appetite	35 (70)	0	15 (30)
Mood	48 (96)	0	2 (4)

Side effects of treatment

The side effects of MM use were infrequent and without recognizable sequalae for the long-term follow-up. Most side effects were connected to the smoking mode of delivery of MM. Five (10%) patients who smoked reported a burning in their throat and anxiety attacks; 4% reported stomach pain but it was not clear if these complaints were caused by MM or children's medical condition. In both cases, these complaints rapidly subsided after the administration of H2 inhibitors, and one child stopped treatment with cannabis after the first several doses because of extreme fatigue and slight disorientation. The parents of the children and the children themselves who used cannabis oil did not report any side effects.

During the post-BMT period, levels of cyclosporine and sirolimus were regularly measured and drug doses corrected according to obtained results. We did not note any significant deviations in these drug level measurements among children who concurrently received MM in comparison with those who did not receive MM after stem cells return. Therefore, we were not able to note any effect of MM of anti-GVHD drug levels.

All patients who received high-dose chemotherapy and underwent BMT received MM in the form of orally administered oil drops. No increase in pulmonary aspergillosis was noted among these patients, nor among those who received MM via smoking or by vaporization.

Discussion

Our study shows that the use of MM in pediatric oncology patients may be safe and efficacious, with the potential for lessening the intensity of a child's physical and psychological suffering, thus improving the quality-of-life for this challenging patient population.

The bulk of literature about the use of MM in patients with various diseases, including pediatric oncology, has been continuously growing [6]. There are no absolute contraindications for MM use but certain precautions should be taken into account while considering MM as a therapeutic drug, including a personal and family history of psychiatric disorders, since it is known that such components of marijuana as delta-9-tetrahydrocannabinol (Δ9-THC) may exert their psychoactive properties in an undesired manner in persons who already have some psychiatric disorders [7]. Certain precautions should also be undertaken when administering MM concurrently with other drugs that are metabolized by the cytochrome p450 enzymatic pathway. Certain anticonvulsive drugs given concurrently with MM may lead to an unexpected increase in plasma levels of MM products, thus provoking undesired side effects [8]. Some of our patients,

especially those with brain tumors, received MM concurrently with anticonvulsive drugs. Although we did not perform pharmacological studies directed at the measurement of the plasma levels of MM products, there were no clinical suspicions that possible negative interactions were taking place. There also was no clinical evidence that MM influenced the therapeutic level of anticonvulsive drugs since no new seizures or alterations in the established pattern of existing seizures were noted.

Another issue that may raise concern about the clinical efficacy of MM in pediatric oncology patients is the availability of MM delivered by different ways. It is usually accepted that the bioavailability of orally administered MM is rather low, not reaching even 20% [9–11]. This fact, in part, may explain why systemic side effects of MM in our patients were practically absent, since about 60% of them used the oral route of administration. When MM is delivered by smoking, bioavailability is improved and may be as high as 45% [12, 13].

The side effects noted in our cohort of patients were usually mild and short-term, and most were associated with smoking. As soon as these patients stopped inhaling cannabis smoke, the unpleasant sensations disappeared.

The main concern regarding the use of MM in children is its possible adverse effect on future cognitive and emotional development. It has been documented that cannabis use in young age may negatively affect cognitive functions in the future when compared with a peer-matched population never exposed to this substance [14]. On the other hand, it has been shown that using MM aimed at the control of many distressing symptoms in young patients may actually facilitate cognitive function improvement, at least in the short term [15]. The impact of cannabis use on future cognitive functions in adolescents and young adults is still pending clarification since, in at least one study [16], marijuana-using twins failed to show a significantly greater IQ decline relative to their siblings who had never been exposed to cannabis. It is probable that social and other external factors may play a significant role in young persons who use marijuana in attaining lower IQ levels than expected. It is of interest that, for younger patients, emerging published data indicates that there are significant concerns about how potentially detrimental the prolonged use of cannabis (and other illicit drugs) can be (i.e., those who are younger teens and especially those who are pre-pubertal). Substance abusers had significantly less frontal white matter volume percentage than controls [17]. Since untoward neuropsychiatric effects of cannabis are caused almost exclusively by the TCH component, of which MM has relatively low concentrations, acute toxicity symptoms of cannabis use, such as hallucinations, anxiety attacks, and disorientation, are practically not encountered. We have not witnessed any undesired neuropsychiatric effects of MM in our cohort of patients.

We are aware that some parents seek MM with relatively high concentration of THC since online parent support groups suggest that higher doses of THC are needed for anti-neoplastic effects. However, in the current case study, most of the patients used low THC products and those with higher doses used small doses of rich-THC products and did not reach the high levels and dose of rich-THC cannabis that is recommended in those online groups.

The other concern of the prolonged use of MM is its possible cancerogenic effect. Cannabis and tobacco smoke both contain chemical components, such as benzene, arsenic, formaldehyde, lead, and possibly other potentially cancerogenic constituents

[18]. The concentration of these substances becomes practically undetectable when MM is delivered to the patient via the vaporization route [19]. Vaporized cannabis has been shown to cause respiratory fungal infections in immunocompromised patients, thus it may still pose a danger [20].

There have not been any published data clearly showing that the use of cannabis may cause cancer in humans. The data that suggest such a possibility are of limited value, since other confounded factors, such as tobacco smoking and possible other environmental hazards, make the analysis very difficult and the results equivocal [21, 22]. There have been no reports published so far on an association between the use of cannabis for medical purposes and the subsequent development of cancer. We were also unable to locate any publications assessing the cancer risk of the oral consumption of cannabis and an increased risk of any form of gastrointestinal cancer or any other form of cancer. The data on the possible role of cannabis as a causative agent in pediatric oncology are lacking also. Most of our patients who received MM were using the oral route with oil drops, while some others were using vaporized MM in the form of inhalation. Given the progressive nature of cancer and the circumstances in which MM was used, we felt that this theoretical, even if possible, cancerogenic effect of this kind of treatment was negligible for this cohort of patients.

Since our questionnaire was not formally validated, thus creating possibility of bias in the results, our main and primary aim was to elucidate what parents and children think about MM and its role as another drug directed at better controlling physical and psychological symptoms.

Generally, children and parents reported their satisfaction with MM treatment, mentioning improvement in appetite, mood and sleep pattern. The effect of MM on pain was more difficult to ascertain, since all the children continued to receive other analgesics along with their MM treatment.

It is especially noteworthy that five of our patients were receiving MM while undergoing bone marrow transplantation while being treated with many other drugs concurrently. Reports on the effects of MM therapy from these patients and their parents were positive. Although we did not specifically look at the impact of MM on liver and kidney functions, we did not note any significant laboratory anomalies that could be specifically attributed to MM treatment.

We aware that our study is not without several and sometimes substantial drawbacks. First, the lack of validated quality-of-life scoring or other validated symptom scoring tools to actually show benefit to the individual patients makes our study less credible in terms of efficacy and toxicity assessment, since there is the potential of significant bias by simply asking the patient whether he/she thinks the drug has been helpful. One also cannot exclude a 'placebo' effect that could result in the families thinking there is a benefit.

In conclusion, medical cannabis may be potentially useful as a complementary therapy to the conventional supportive medical treatment of a child with cancer. In addition, MM therapy should be considered for pediatric cancer patients suffering from poorly controlled symptoms (both physical and psychological), even when death is not imminent but may be likely in the future. Taking into account that we have a profound deficit of knowledge on the possible unwanted consequences of the prolonged use of

MM in the pediatric population, further research in this field is needed. Before declaring MM as a safe and effective treatment in pediatric oncology patients and in order to make MM an integral part of supportive care, further studies are needed to learn about optimal dosing, way of administration and efficacy. More data should be accumulated about the short- and long-term toxicity of MM. For these purposes, we need proper research funding and support for clinical randomized trials to understand how to use MM in a more rational and scientifically based manner.

Declaration of interest

No potential conflict of interest was reported by the authors.

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