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CANNABINOIDS IN ONCOLOGY

Cannabis is one of the oldest and most widely used medications in traditional medicine. It was used millennia ago by civilizations in Asia, The Middle East and also by the ancient Greeks and Romans. Later its usage spread to other parts of the world. What followed was expulsion of cannabis from medicine in the 1940's. It was classified as a harmful substance without medicinal properties. This began the systematic stigmatization and repression, all use in medicine and research was stopped.

Now, after multiple decades of prohibition by law, cannabis is making a return to medicinal use. More and more studies show potential healing properties, beneficial in numerous fields of medicine and refute the high probability of addiction. Changes have started in legislation and classification of cannabis, but they are still unjustifiably slow.

Some gradual changes were also made in Slovenia. Now the country has a modern legislation on use of cannabinoids in medicine, which, alongside phytocannabinoids and synthetic cannabinoids, also permits the use of medicinal cannabis. On the other hand, a steady supply of pharmacies and uninterrupted therapy are still not taken care of. The products available on the market include Dronabinol (synthetic THC analogue) and Cannabidiol (synthetic or extracted from plants), all in the form of oral drops.

In oncology, cannabinoid-based medications are used for alleviation of symptoms of advanced malignant disease, as an addition to standard medication (add-on therapy). They are prescribed to patients with symptoms that are harder to manage, with multiple symptoms, or at unacceptable adverse effects of standard therapy. Cannabinoid-based medications have many specifics: addition of cannabinoids to standard medications in many cases increases the effect of these medications or produces same effect at lower doses of the standard medications, which decreases the adverse effects of those medications (ie. opioids), when choosing the cannabinoid-based medication, we take advantage of positive mutual effect in the form of increased efficacy (entourage effect) and lessening of adverse effects (ie. addition of CBD to THC). The use of the whole plant is thus more effective than the use of individual cannabinoids due to inclusion of the whole palette of its bioactive substances.

As a rule, symptoms of advanced malignant disease appear in bundles and are interdependent. For example, pain is usually accompanied by weight loss, insomnia, depression, cognitive decline and chronic fatigue. Cannabinoids as an addition to analgesic therapy with opioids increase the analgesic effect in chronic, especially neuropathic pain, have a positive effect on neuropsychological symptoms, such as anxiety and insomnia, as well as having an effect on loss of appetite, weight loss, nausea, vomiting and skin itching. Studies have shown that chronic inflammation due to an advanced malignant disease is the cause for most of the symptoms of said disease. By affecting the inflammation, cannabinoids have an important effect the symptoms, additionally, curtailing the inflammatory response can slow down the malignant growth.

Cannabis also has some pharmacokinetic specifics. The effective dose varies greatly from individual to individual, thus the treatment must be individualized. Doctor supervision is required over the effectiveness, adverse events and the course of the malignant disease.

ANTITUMOR THERAPY

Evidence shows that tumor tissue in many kinds of cancer has overexpressed cannabinoid receptors. Activation of these receptors by cannabinoids inhibits uncontrolled cell proliferation, ability to migrate through the body (metastasis), creating new blood supply (angiogenesis), and can even cause the death of tumor cells (apoptosis).

The role of the immune system in fighting the malignant cells is being highlighted more and more. Nobel Prize in Physiology or Medicine 2018 was awarded to immunologists James P. Allison and Tasuku Honjo, who developed a new cancer treatment, based on stimulating the immune system's defensive capabilities (immunotherapy). Also in this aspect cannabinoids have an important role, due to a high density of cannabinoid receptors on the immune cells.

The strength of evidence needed for use of cannabinoids as an antineoplastic medication is still lacking, but there are many studies being carried out on this topic, including clinical studies, that show a potential future role of cannabinoid receptors as one of the targets for a combined treatment of cancer (synergistic with standard systemic therapy and alleviation of adverse effects of systemic treatment).

The widespread expectations of miraculous healing effects are thus still unrealistic. Treatment of cancer with cannabinoid cannot replace the standard multimodal therapy (surgery, systemic pharmacological therapy, radiation). The greatest danger lies in self-medication with cannabinoid products, such as hash oil, replacing professional oncological treatment in curable cancers, because every delay in effective treatment critically decreases the chances of curing the disease. Treatment with cannabinoids requires a high level of expert knowledge on receptor distribution in individual tissues, correct proportions of individual cannabinoids for treatment of specific kinds of cancer, dosing and potential contraindications because of existing forms of treatment. The doctors often see cases, where cannabinoids could have a beneficial effect, but that is absent due to the patient's and black market seller's lack of proper knowledge on the disease, the effects of the treatment and also the responsibility for selling contestable products.

OBSTACLES FOR USING CANNABINOIDS IN TREATMENT

- Cannabis still carries the stigma of an ineffective medication and a dangerous drug. The prejudices and outdated ideological obstacles are still present, which invalidates the up-to-date legislation, because it is not used to any effect. No application for a marketing license for medicinal cannabis was approved, because none satisfied the endless (unnecessary) administrative requirements.
- The changes in legislation also had little to no effect within the medical circles. The knowledge of medical professionals is still greatly lacking, there is no systematic education, the topic is practically absent in medical and nursing curriculums (in a survey, carried out in 2015 among healthcare professionals, more than 90% of participants answered that they needed more knowledge on this topic). There is a lack of professional guidelines for use of cannabinoids in medicine. Doctors are consequently worried about potential danger of adverse effects and thus well-meaningly hesitant to prescribe cannabinoid-containing medications.
- The decisions on use of cannabinoids are still influenced by results of older clinical studies, where medicinal effects of cannabinoids were compared to those of standard medications, which were greater. Consequently, the opinion that introduction of cannabinoids is not needed because more effective standard medications is available, still persists. But this position ignores the adverse effects of these medications, which are often greater than those of cannabinoids, and the fact that no medication is effective for all patients with the same indication. But these reasons make add-on medications very important.
Newer comparison studies on add-on therapeutic potential of cannabinoids show evidence that addition of cannabinoids (or cannabis) provides benefits in management of multiple symptoms and decrease in adverse effects of standard medications. For example in a study published this year, which included almost 3000 patients with an advanced malignant disease, indicated that cannabis is a medication that is well-tolerated, effective and safe option for treatment of multiple symptoms in palliative medicine.
- The discussion of use in medicine is often confounded with the discussion of legal status of non-medicinal use, which should not be the case.

CONCLUSION

Malignant diseases are very heterogeneous, so treatment of both the underlying disease and its symptoms always combines multiple kinds of treatment and multiple medications within pharmacological treatment – the treatment is multimodal. Cannabinoids present an important addition to the existing arsenal of standard medications, increase the likelihood of optimal management of symptoms and course of the disease and improve the quality of life for a certain segment of patients. Slovenia has an appropriate legislation on use of cannabinoids in medicine, but implementation in

clinical use is still hindered by outdated stigmatization of ineffectiveness, addiction potential and harmfulness, which formed in decades of consideration exclusively in the context of recreational use.

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