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Original paper

The management of strong opioid-induced constipation in neoplastic patients

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Abstract Patients who undergo intensive treatments with high doses of opiates will be confronted with opiate-induced constipation at a certain point during the treatment. This aspect, the presence of medication-induced constipation, significantly alters the quality of life in a negative way. From the very beginning of the opioid treatment initiation, patients should be warned about and they should become aware of the potential adverse effects of these medications, since constipation has a strong psychological impact. As a palliative treatment, laxatives should be administered from the first day of the opioid treatment.

Keywords Cancer pain, strong opiates, constipation.

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Introduction

Whether it is a somatic, a visceral or a neuropathic pain syndrome, it is highly prevalent among cancer patients LI & al [1]. Studies show that approximately 90% of the patients diagnosed with this pathology develop episodes of pain at a certain point in the evolution of the disease, most of whom require strong 3rd degree analgesia, and also strong opioid treatment TRESCOT [2]. However, despite their efficiency as an analgesic therapy, opioids determine a series of adverse reactions, such as gastro-intestinal. Constipation is the most common of all DORN & al [3].

The occurrence of opioid-induced constipation can be physio-pathologically explained through the fact that these substances impair the normal functions at the level of the digestive tract, primarily by inhibiting peristalsis and gastrointestinal motility, secondly, by the tonic spastic action at the level of the intestinal and colon muscles, and thirdly by inhibiting the electrolyte secretion by favoring water retention, and last but not least, by the dysfunction they cause in the anal sphincter, action which contributes to the clinical picture manifested through the sensation of anal blockage and incomplete defecation HOLZER [4], KUMAR & al [5], KURZ & al [6].

By making a cause-effect connection between the two above-mentioned ideas, it could be stated that most of the patients confront themselves with opioid-induced constipation at a certain point. It represents a major problem among neoplastic patients, because it significantly alters the quality of life in a negative way BELL & al [7]. Moreover, there are studies which have monitored pain-determined stress and constipation-determined stress, which concluded that pain is less stressful for the patient compared with the constipation induced during the treatment for pain HOLMEZ [8], RUMMAN & al [9] TIGLIS & al [10]. This sometimes determines the patient not to be compliant with the analgesic treatment, to interrupt it, thus entering the vicious circle in which he feels pain without opioids or he has constipation with opioids BALMUS & al [11] DOBRICA & al [12]. The main question that arises on this subject refers to the correct management of strong opioid-induced constipation.

Material and Methods

A group of patients undergoing treatment with strong opioids was admitted to the Chronic Oncology-Palliative Care Unit of "Saint Luca" Hospital in Bucharest.

A number of 160 patients was assessed and then a strong opioid treatment for severe pain was initiated. Out of these, 70 patients had also breakthrough pain, which required the administration of two opioids.

These patients were admitted into the department between January 1st and July 1st, 2017. They signed the informed consent. The study was approved by the ethical board of "Saint Luca" Hospital. The data were analyzed in SPPS.

Results

The minimum age of the group was 29 years, the maximum - 87 years, the average (± sd) 62.5 (± 10.5) years. The age and the gender distribution can be seen in Figure 1.

The classification by types of cancer showed that more than 73% of the patients had lung cancer, as seen in Figure 2.

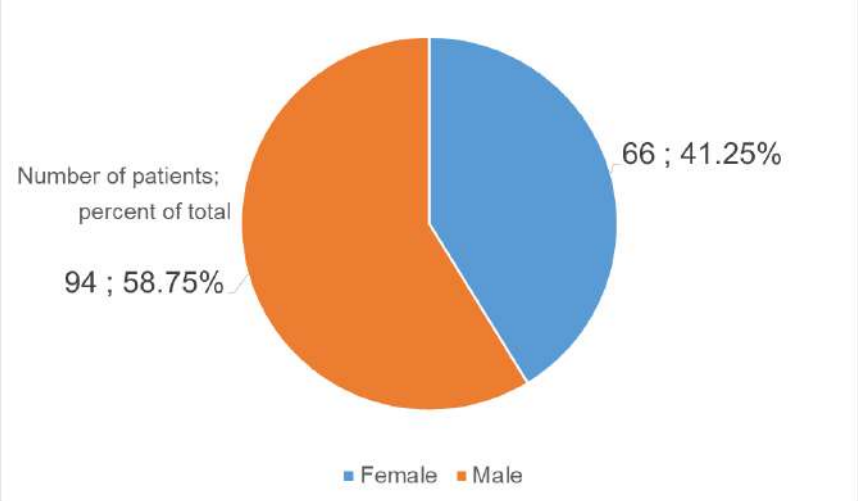

Figure 1. Distribution groups by gender

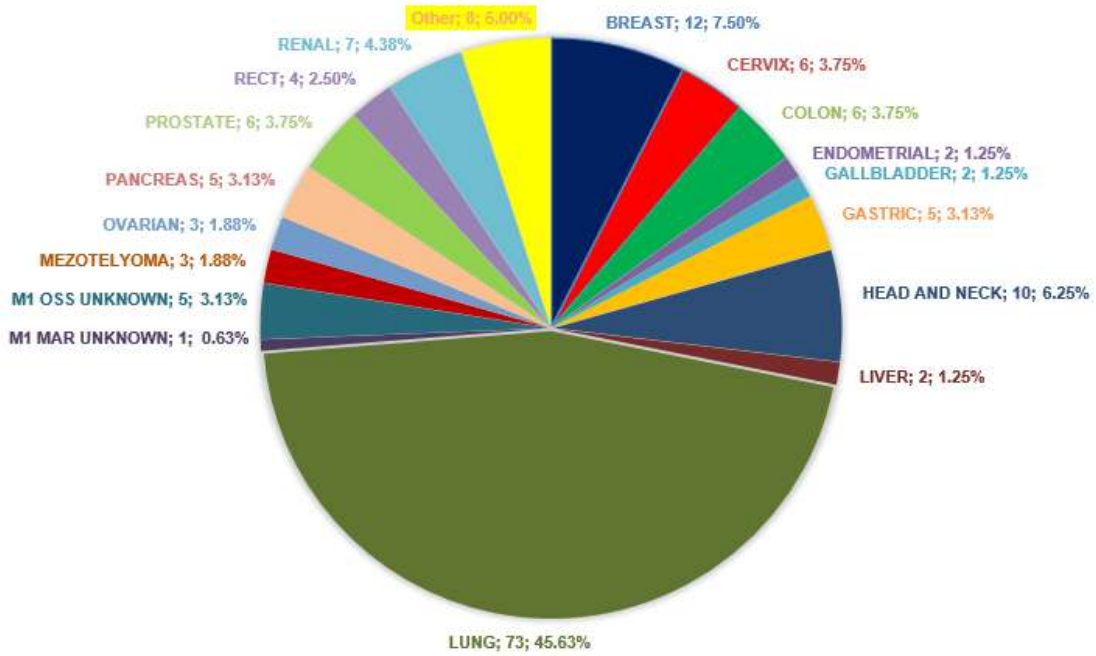

Figure 2. Distribution of types of cancer.

Following the application of the ECOG Scale of Performance Status questionnaire, which evaluated the impact of the disease on the quality of life of the neoplastic patient, 63.75% of the patients had a score of 3 indicating a limitation of normal daily activity and limited self-care capacity. On the other hand, as seen in Figure 3, 28.13% of the patients were assessed with score 4, this being the most severe degree if we do not take into account the death score of 5.

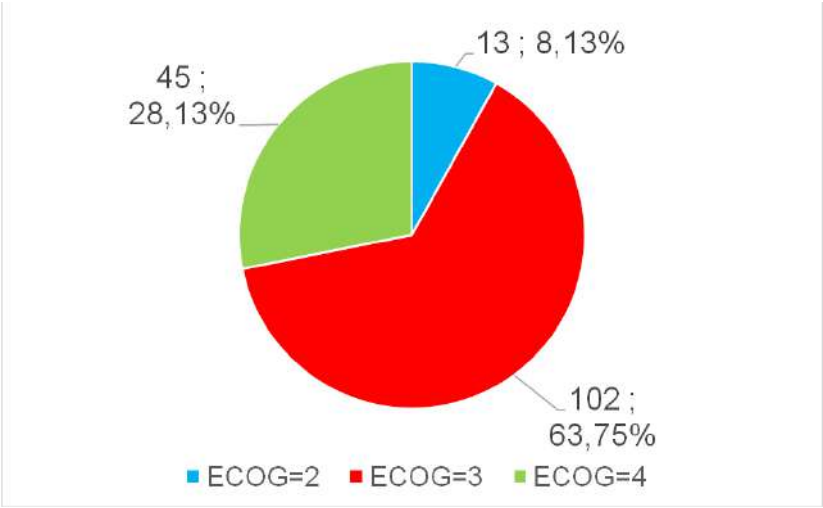

Figure 3. ECOG performance status score distribution

Strong opioids used for the treatment of chronic severe pain were: morphine, fentanyl patch and slow-release tablets (oxycodone, morphine sulphate, morphine hydrochloride), morphine or immediate-release tablets (morphine sulphate or fentanyl) were added for breakthrough pain (BTP).

The prevention of constipation was done through the association of a laxative treatment and physical measures (diet, hydration and ambulation) from the first day of major opioid treatment initiation.

The intensity of constipation was evaluated, according to The Edmonton Symptom Assessment System (ESAS) (other symptoms – constipation). ESAS is a screening tool in the oncology department of "Saint Luca" Hospital. One week after treatment initiation and also 3 weeks after treatment initiation, the score given was: 0=without constipation, 1-3=low-intensity constipation, 4-6=moderate-intensity constipation, 7-10=high-intensity constipation BRUERA & al [13].

The laxative used at the beginning of the treatment was lactulose, in a dose of 10-20 g (15-30 ml/day). The patients who presented high and moderate-intensity constipation one week after the initiation of the treatment were also given bisacodyl 5-10 mg/day.

The patients who were constant in high-intensity constipation under two laxatives were also given micro-enemas so that they could defecate every 4 days at most.

As for the treatment of chronic high-intensity pain, 90 patients underwent treatment with one major opioid, while 70 patients also received a second major opioid for the treatment of breakthrough pain, as seen in Figure 4.

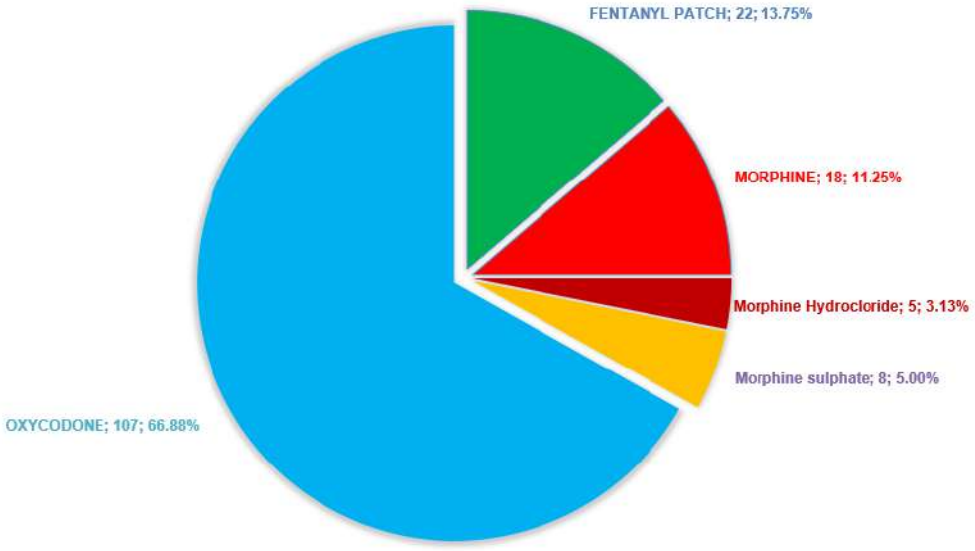

Figure 4. Distribution of patients after morphine or opioids taken for chronic pain.

The doses of major opioids used in the treatment of chronic pain were: morphine (20 mg - 120 mg/day), fentanyl patch (25 micrograms - 150 micrograms every 72 h), oxycodone (40 mg - 200 mg/day), slow-release morphine sulphate (60 mg - 180 mg/day), morphine hydrochloride (60 mg - 300 mg/day) (Figure 5).

The doses of major opioids for breakthrough pain (BTP) were: morphine (20 mg - 40 mg/day), fentanyl-immediate-release tablets (300-900 micrograms/day), immediate-release morphine sulphate (20-80 mg/day), see Figure 6.

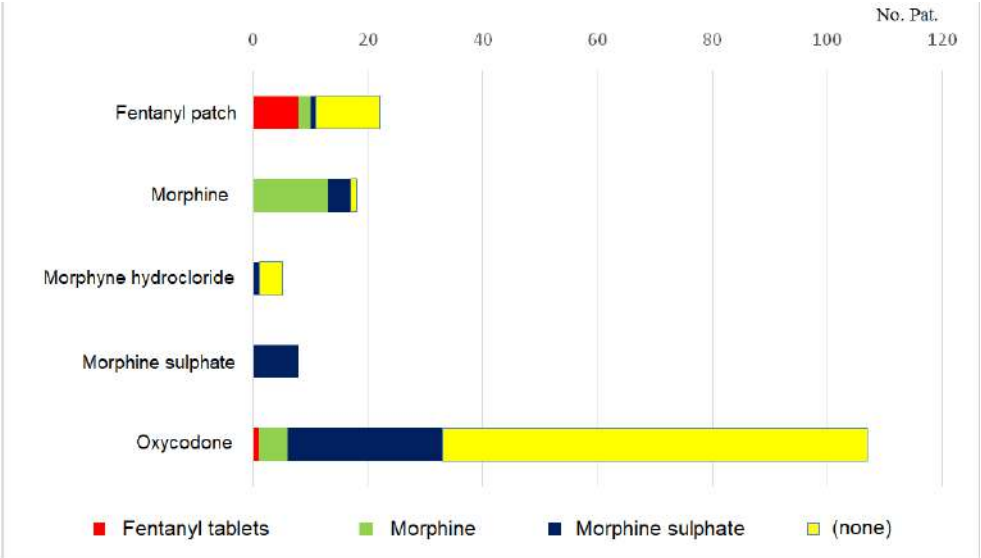

Figure 5. The doses of major opioids used in the treatment of chronic pain.

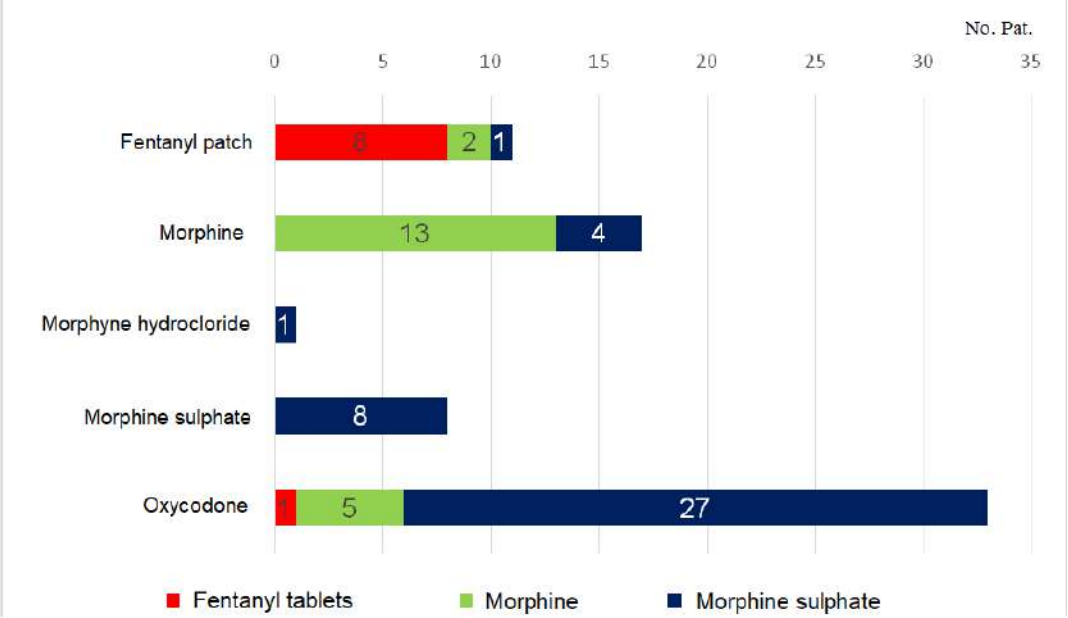

Figure 6. The doses of major opioids for breakthrough pain (BTP).

One week after treatment initiation with lactulose, the distribution of patients according to the intensity of constipation was: severe – 32 patients, moderate – 49 patients, low – 55 patients, while 24 patients were not constipated at all. (Figures 7, 8)

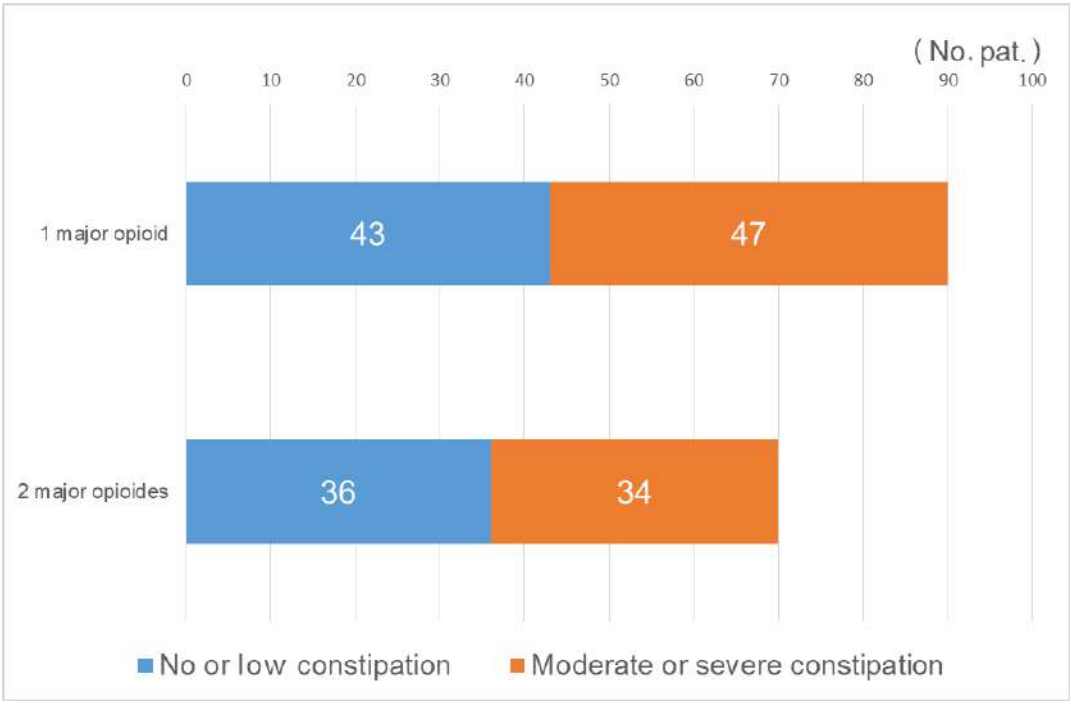

Figure 7. Distribution of patients according to the intensity of moderate constipation, after one week of treatment with lactulose.

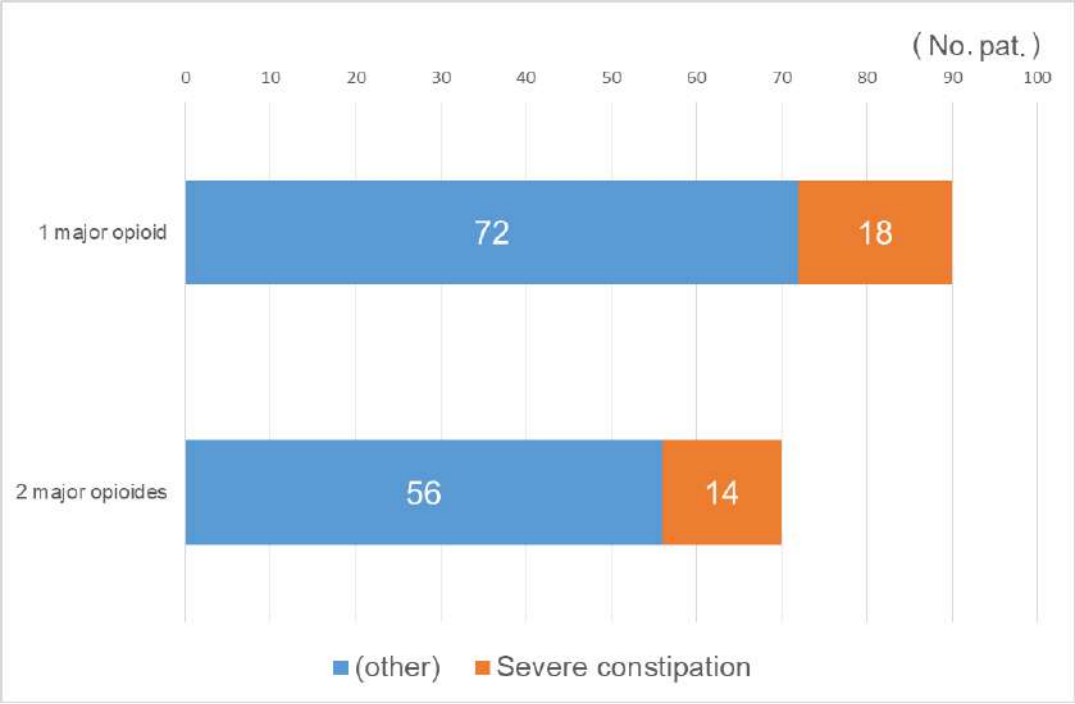

Figure 8. Distribution of patients according to the intensity of severe constipation, after one week of treatment with lactulose.

Three weeks after treatment initiation, under treatment with lactulose, among the patients with low-intensity constipation or no constipation at all and under treatment with lactulose and bisacodyl, and among the patients with moderate or high-intensity constipation, the distribution of patients according to the intensity of the constipation was: severe – 16 patients, moderate – 46 patients, low – 74 patients, while 24 patients were not constipated at all. These results can be found in Figures 9, 10, 11.

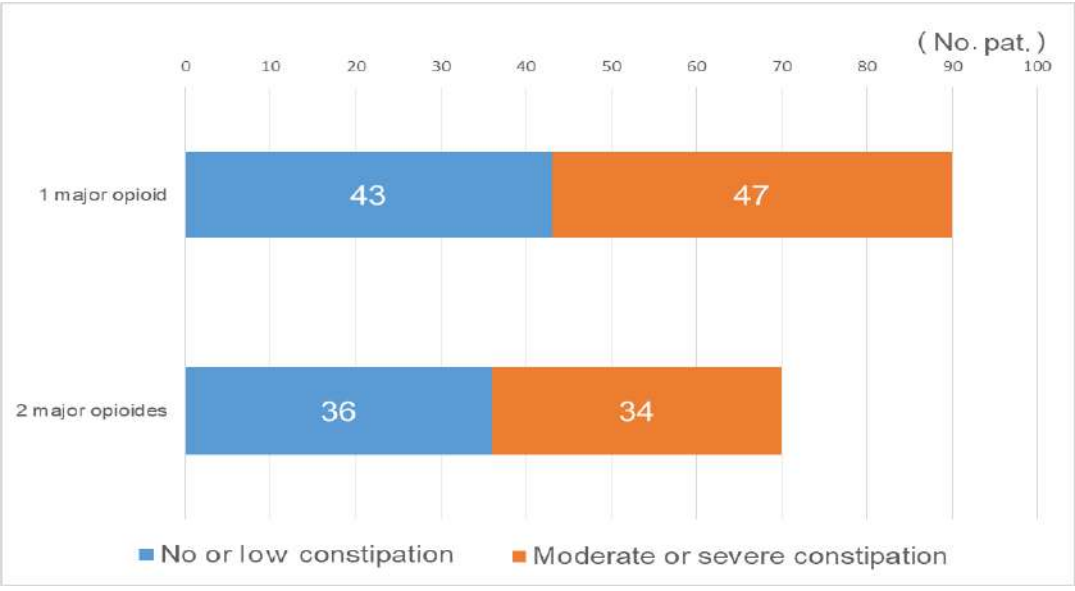

Figure 9. Distribution of patients according to the intensity of the constipation-moderate after 3 weeks of treatment with lactulose.

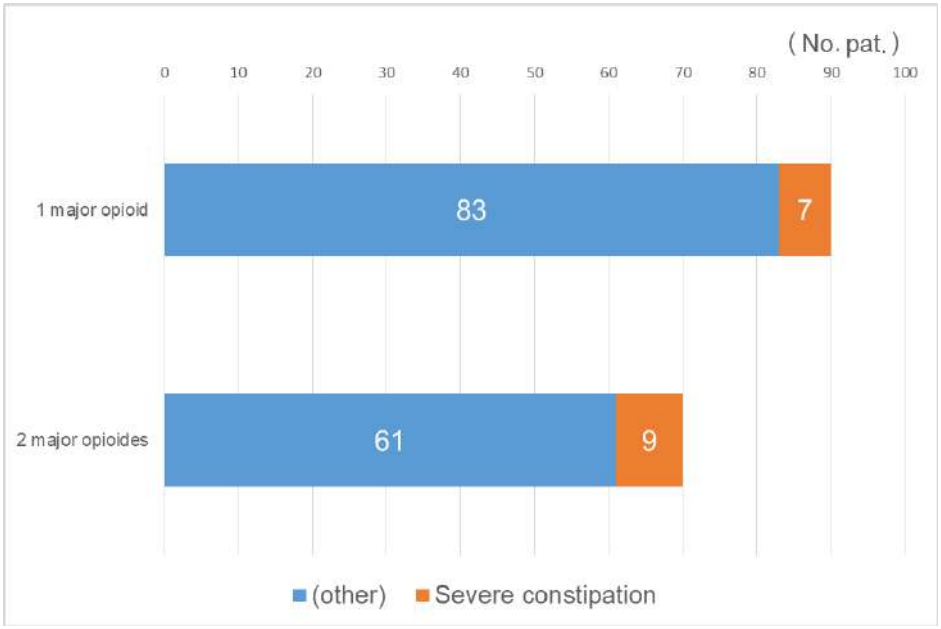

Figure 10. Distribution of patients according to the intensity of the constipation-moderate after 3 weeks of treatment with lactulose.

Micro-enemas were recommended to the 16 patients with high-intensity constipation after 3 weeks of treatment with 2 laxatives.

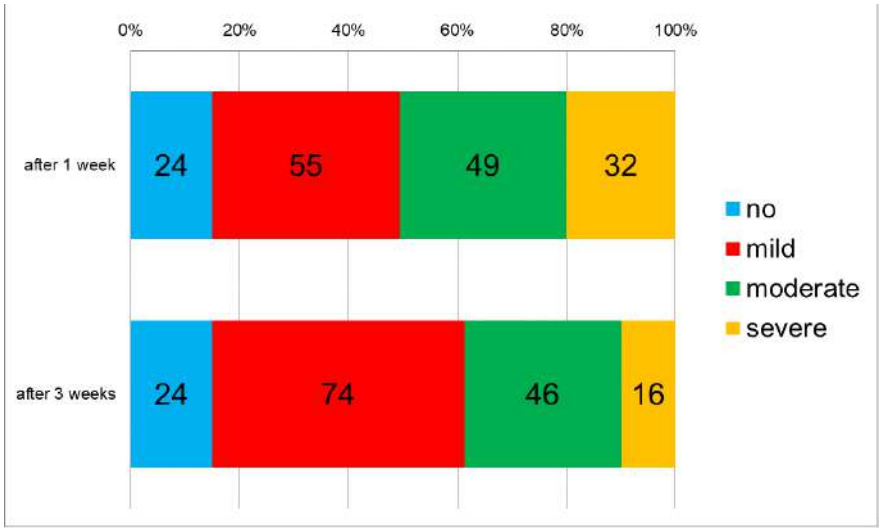

Figure 11. Assessment of constipation in all patients.

Patients in whom the intensity of constipation increased from low to moderate after 3 weeks of treatment with lactulose were also given bisacodyl, while in patients for whom the intensity of constipation decreased from moderate to low, under the association of two laxatives, the treatment was constant.

Discussion

According to WHO, strong opioids are indicated for moderate to severe pain, respectively for the 3rd degree of pain, when analgesia is no longer achieved through low opioid treatment. Moreover, there are studies that have shown the efficacy of these drugs also in the treatment of dyspnea in patients with pulmonary neoplasia MAZILU & al [14] PARASCHIV & al [15]. Opioids are subdivided into two classes, namely morphine and morphine-like substances. Morphine can be administered both parenterally (fast-release vials) and orally, under the form of tablets, respectively morphine sulphate (both fast-release and slow-release tablets) and hydrochloric morphine (slow-release tablets), morphine-like preparations are:

oxycodone (fast-release and slow-release tablets), fentanyl (under the form of slow-release plasters or fast-release tablets), hydromorphone, and methadone PORTENOY [16].

Morphine is considered the gold standard in the treatment of neoplastic pain, but, there is no evidence to prove its superiority regarding the safety, the adverse effects or analgesia compared to other strong opioids. Therefore, the right choice for each patient cannot be foreseen, the relationship efficacy/safety/adverse reactions cannot be known before treatment initiation, and it is the clinician who will have to decide what medication of choice to elect first, based on his clinical experience and availability PORTENOY [17], BRATU & al [18].

Patients should be warned from the beginning about the opioid treatment to acknowledge the potential adverse effects of these drugs. Since constipation has a strong psychological impact on patients, they should know about its risks of occurrence in order to prevent or, at least, to lower the risk of affecting the quality of life.

The therapeutic measures of constipation are both non-pharmacological and pharmacological. As to the approach from the lifestyle point of view, patients should be advised to have a good hydration, a fiber-rich diet and to do regular physical exercises VONDERHOLZER & al [19]. Other non-pharmacological options are giving up opioid therapy, which is not desirable, or the rotation of opioids, which has also proven not efficient in improving the gastrointestinal adverse reactions LIU [20], MOCAN & al [21].

The ultimate and the most important approach is the pharmacological treatment of constipation. A wide variety of laxatives are used to treat constipation.

The guidelines of the European Association of Palliative Care (EAPC) recommend the administration of a laxative from the very beginning of the opioid treatment. Practically, this adverse reaction seems to be so common (in approximately 90% of the patients) that a preventive measure against constipation is required CARACENI & al [22]. There is no evidence to support a clear answer regarding the efficacy of a laxative compared to another for cancer patients in case a question about the laxative of choice might be asked. Studies in the literature state, however, that the association of two laxatives with different mechanisms of action has proven more efficient than the administration of a single laxative, especially in case of constipation refractory to treatment LIU [19], MAZILU & al [23]. The most common combination of laxatives is the association of a stimulant such as bisacodyl with a laxative which determines the increase of the fecal bolus, thus decreasing its consistency and determining intestinal lubrication, such as lactulose or sodium docusate MOCAN & al [20].

From the point of view of adverse reactions, laxatives are generally well-tolerated, but they can also cause nausea, vomiting, diarrhea, abdominal pain, a condition that requires the interruption of the treatment if it cannot be controlled CANDY & al [24], CIUHU & al [25]. Moreover, taking into account the fact that laxatives do not address the mechanism by which opioid-induced constipation occurs, sometimes, its control is impossible to achieve AMMEDZAI [26], YIPEL & al [27], VAN DEN BEUREN & al [28], CIOCIRLAN & al [29]. Therefore, it seems that strategies like opioid-antagonist therapy (methylnaltrexone, naloxone) could prove more efficient for such reasons, but they are not available nor used by clinicians as routine methods in all countries.

Conclusions

The prevalence of pain among cancer patients is very high, irrespective of the stage of the disease. Strong opioid therapy is the gold standard in the control of moderate to severe pain (3rd degree WHO). The oral administration is preferable, and there are a variety of substances, from morphine to similar preparations such as Oxycodone, Fentanyl, etc.

Constipation should be seriously taken into account and should be approached through preventive measures, which consist in changing the lifestyle through a rich-fiber diet, good hydration, regular physical exercises and pharmacological methods, such as the administration of a laxative or a combination of laxatives from the beginning of the analgesic treatment.

The most commonly used laxatives are those with osmotic action, such as mannitol/ lactulose, and the stimulant ones, such as bisacodyl.

Acknowledgment

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