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Chemotherapy-induced polyneuropathy (CIPN) is a frequent complication of causative therapy for cancer. The frequency of occurrence of this phenomenon implies the necessity to consider all the possible methods of treatment. The main medications are antiepileptic drugs and antidepressants; however, opioids constitute an integral part of a complex therapy in this nosological unit. The presented report is an attempt to evaluate the current knowledge concerning the role of opioids in the treatment of CIPN.

Due to the lack of studies concerning the application of opioids in CIPN, conclusions concerning their effectiveness may be drawn only by analogy. Based on the literature available concerning model experiments and clinical observations, it may be presumed that opioids are important components of complex therapy in the case of neuropathic pain; thus they are also efficient during the treatment of chemotherapy-induced polyneuropathy. Affinity to membrane receptors is among the preconditions of the analgesic effect of opioid drugs. The variety of these proteins and their subclasses determines the various effectiveness of their ligands, which justifies both opioid rotation and binding. Based on model studies and clinical observations, it was noted that from among pure opioid receptor agonists, oxycodone showed the strongest analgesic activity in neuropathic pain.

Key words: chemotherapy-induced polyneuropathy, neuropathic pain, cancer pain management, opioids, side effects.

Opioids in the treatment of chemotherapy-induced polyneuropathy

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Introduction

The primary task in the development of oncology is to increase the effectiveness of treatment by introducing new forms of chemotherapy, radiotherapy, hormone therapy and surgical techniques. Due to this, it is possible to inhibit the development of a cancerous disease, as well as to increase patients' cure and survival rates. One of the consequences of the advancement in treatment is the use of increasingly more toxic drugs, which act on all cells of the body. The side-effects of anti-cancer therapy depend mainly on the specific action of the drug and are located in various organs [1]. The prognoses indicate an increasing number of cancer cases diagnosed; therefore, with an increased cure rate it may be anticipated that the number of patients suffering from the side-effects of drugs will also be higher [2]. The presented report is an attempt to present the problem of the application of opioids in a relatively frequent syndrome – chemotherapy-induced polyneuropathy (CIPN).

Reports devoted to the problem of neuropathy most often classify this disease by distinguishing the primary causes of the development of nerve lesions [3-8], while the problem of the impairment of nerves in the course of chemotherapy is approached rather marginally. Polyneuropathy in the course of diabetes and postherpetic neuralgia are best investigated and described; therefore, very frequently also the experiences obtained during the treatment of these syndromes are referred to CIPN [5, 7, 9, 10].

Publications concerning evidence-based medicine (EBM) do not contain any mention of CIPN pathophysiology and treatment [7, 10, 11], whereas in the reports discussing specified groups of chemotherapeutics, information may be found which allows the evaluation of this problem limited to the selected group of drugs, and not of the problem as a whole [12, 13]. Finnerup *et al.* suggest that if there is no knowledge available concerning pathophysiology and methods for prevention of the phenomenon described, one should at least strive to discover a method of treatment of arduous symptoms [7].

Toxic neuropathy

Among the causes of the occurrence of the peripheral nervous system pathology is the toxic activity of various chemicals, hence the term toxic neuropathy (TN). Drugs from the group of chemotherapeutics should also be classified into toxic substances; thus, CIPN is one of the forms of TN [14]. Attention should be paid to the fact that very frequently CIPN is considered as a pathological syndrome of a uniform aetiology and symptomatology. In fact, only the symptoms of CIPN in the form of the sensation of numbness, tingling (pins and needles), burning pain, shooting or stabbing, are the common characteristics for all drug-induced pain syndromes, while the pathomechanism of this phenomenon is varied. Studies of the problem described are continuing, and at least in the case of selected drugs it is already possi-

ble to describe the pathomechanism of nerve lesion [14, 15]. The mechanism of neurological damage will be thoroughly discussed in a separate article. Despite the fact that neurotoxicity of these preparations and the frequency of inducing CIPN are known, to date efficient methods of preventing this phenomenon have not been found [5, 14, 16, 17].

In the majority of cases, the occurrence of changes in the nervous system caused by chemotherapy depends on the cumulative dose of the drug, while the onset of the disease may occur both during the treatment and after its completion. Table 1 presents a compilation of selected characteristics and prevalence of CIPN, but data on this subject are inconclusive.

CIPN treatment

The principles of treatment of neuropathic pain were encoded in the guidelines published by various scientific associations, and the majority of them were based on the EBM. All the guidelines available recommend antidepressants and antiepileptic drugs as the most effective, and consequently, recommended as first-line drugs, and opioids are classified in second place [4, 6, 18, 19]. It is also recommended adjuvant therapy, for the use of topical lidocaine, or capsaicin in the form of patches. There is some controversy concerning the method of justification for the introduction to treatment and dosage method [18, 19]; nevertheless, these problems exceed the scope of the presented report and require a separate discussion.

As mentioned at the beginning, there are no unequivocal data from randomized clinical trials which would classify opioids used in the treatment of painful neuropathy caused by chemotherapy. The use of these drugs is approached in various ways by the authors of guidelines. The cause is the sole essence of the pain syndrome discussed, because it should be approached as mixed neuropathic pain. It is much easier to develop algorithms concerning the selected nosological unit of recognized and defined aetiology and pathogenesis, such as postherpetic neuralgia, diabetic polyneuropathy, or trigeminal neuralgia. Some recommendations [8, 12] assume an introduction into the treatment of solely tramadol, emphasizing, at the same time, that strong opioids should be treated as alternative drugs with respect to their side-effects.

The introduction of opioids into the treatment, in the case when the cause of the disease is primary impairment of the central or peripheral nervous system, may evoke controversy due to the above-described problems. This is obviously problematic, because the most frequent reason for being inhibited, both on the part of the patient and the physician, is not the possibilities of hormonal system disorders, or the supposed effect in the immune system, opioid induced hyperalgesia, but mainly the fear of addiction [20]. This mechanism is so strong that even some physicians who apply these drugs in practice reluctantly introduce them into treatment in the cases of so-called non-cancer pain [21]. In the case of a cancerous disease, very frequently a patient already receives opioids within the therapy, due to experiencing other pain complaints associated with the primary disease which require the routine use of drugs in accordance with the analgesic ladder.

The clinical decision in the case of the treatment of patients in such a situation is of totally different importance, because it does not focus on the problem of 'whether to introduce an opioid', but on 'which opioid will be effective

Table 1. Chemotherapeutic agents known to induce painful peripheral neuropathy. Based on Paice 2011

Drug	Incidence (%)	Symptoms
Carboplatin	5-20	Usually only with higher doses.
Cisplatin	30-100	Dose dependent, may progress for months after treatment discontinued; sensory ataxia with gait dysfunction
Oxaliplatin	85-95[a] 15-20[b]	Cold-induced acute paresthesias and dysaesthesias of hands and feet
Bortezomib	31-55	CIPN is leading cause of discontinuing therapy; dose dependent, may progress for months after treatment discontinued; sensory ataxia with gait dysfunction, impaired proprioception
Docetaxel Paclitaxel Albumin bound paclitaxel	11-64 57-83 73	Symmetrical painful paraesthesia of feet and hands, may progress to legs, decreased proprioception, weakness, ataxia, gait dysfunction; usually resolves in 1– 3 months although may persist
Vinblastine Vincristine Vindesine Vinorelbine	30-47 11-60 30-47 30-47	Symmetrical painful paraesthesia of feet and hands, tingling, weakness, gait dysfunction; can produce cranial neuropathies; weakness with foot drop; may have autonomic changes (20-30%)
Ixabepilone	20-63	Painful paraesthesia and burning; resolves within 4-6 weeks
Lenalidomide Thalidomide	10-23 25-83	Symmetrical tingling or numbness, pain, weakness, sensory ataxia and gait dysfunction

[a]*acute (during infusion)*
[b]*long term*
CIPN – chemotherapy-induced polyneuropathy

in this case'. Therefore, an attempt should be made to provide an answer to two basic questions:

1. Do we have at this moment sufficiently clear reasons to start treatment with an opioid if the occurrence of CIPN may be expected?
2. Which of the pure μ receptor agonists should be used in combined therapy if we deal with a developed form of neuropathy?

Opioids in CIPN

The efficiency of pure μ receptor agonists, evaluated cyclically in the studies by Finnerup concerning neuropathic pain, did not significantly differ during the period 2005-2010 [6, 7] and is very highly evaluated. The NNT index (number needed to treat) for this group of drugs within the last 5 years remained at the level of 2.6 (1.7-6.0), despite the fact that the subsequent results of randomized clinical studies were published. This indicates a high effectiveness of opioids in the treatment of neuropathic pain practically in all its forms. It is also important that the NNH index (number needed to harm) remained at a relatively high level of 17.1 (9.9-66), which is evidence that these drugs are still regarded as relatively safe. Similar conclusions may be drawn based on reports pertaining to the use of tramadol; in this case an increase in NNH was even found from 9.0 (6-18) to 13.3 (8.8-28). However, the author herself pays attention to the fact that the above-mentioned changes were observed based on only two new reports concerning strong opioids and three reports on tramadol. In addition, as mentioned at the beginning, the reports concerned nosological units other than painful neuropathy caused by chemotherapy; therefore, the conclusions with reference to the disease described may be drawn only by analogy.

Eisenberg *et al*. [22, 23] analysed reports concerning the application of opioids in the treatment of various neuropathic pain syndromes which show that the drugs most often investigated were alfentanil, morphine and oxycodone. This report does not provide direct data for the presented considerations, because none of the reports concerns CIPN, and also these drugs are compared to placebo with no crossover comparison. As an analogy, it may be assumed that although the above-mentioned drugs are effective in diabetic polyneuropathy, postherpetic neuralgia and post-stroke pain, its activity in CIPN may also be expected. The authors emphasize that it was observed that opioids are more effective in peripheral neuropathy, by reducing the dynamic mechanical allodynia and cold allodynia, which may suggest their effectiveness in CIPN. While analysing opioids in indications other than CIPN, the researchers make the reservation that further studies in this area are necessary.

There have been published recently both the systemic reports and guidelines of scientific associations approaching the use of strong opioids as an integral part of neuropathy therapy in the course of cancerous diseases. The authors of these publications indicate the lack of literature concerning CIPN; however, they incorporate these drugs into routine therapy [24-26]. Similar suggestions are found in the report by Dzierżanowski and Ciałkowska-Rysz [27]. The researchers (also paying attention to the lack of literature biased towards CIPN) emphasize that the use of opioids may be one of the methods of treatment of this pain syndrome.

Selection of opioid

Knowledge concerning the mechanism of action of opioids has considerably increased during recent decades. Due to this, it is easier to select the most effective drug, both from the aspect of the strength of its activity, possible undesirable effects, and particular clinical situations in which it may be most efficient [28, 29].

In this case, knowledge of the structure and physiology of opioid receptors and G proteins bound to these receptors is of key importance. The above-mentioned membrane structures are characterized by a high changeability, dependent, among other things, on exposure to exogenous ligands. In this paper we present data on opioid receptor agonists, but there are also suggestions for the use of ago-antagonist in this indication.

The occurrence of nervous system cell resistance to the action of opioid analgesics is due, among other things, to the phenomena of internalization and dimerization of the membrane receptors, as well as considerable polymorphism of the G protein responsible for their intracellular activity [30].

Internalization consists in 'submerging' of the receptor in the structure of the cell mucosa, due to which it becomes less sensitive for agonists. Dimerization is the formation of complexes by the combination of two receptors, which act 'sort of together'. For the activation of such a dimer complex, a higher ligand concentration in the extracellular space is required. Similar dimers are formed within various classes of opioid receptors, and may also consist of opioid receptors and other membrane receptors [31]. This justifies the individualization of treatment, because the same drugs may variously act in different patients, and the analgesic effectiveness of opioids may change in time.

The problem of simultaneous administration of drugs from various opioid groups remains controversial. Doubts concerning the justification of such a procedure may be due to the fact that all drugs in this group have a similar capture spot in the form of an opioid receptor. An anti-nociceptive effect was associated mainly with the μ receptor, whereas at present it has been confirmed that many drugs act through δ or κ receptors, or show activity with respect to many main receptor classes. The change in attitude towards this problem has also been caused by the discovery of subclasses of opioid receptors, which allowed the presumption that the differences in the effectiveness of various drugs in analgesic therapy may be due to affinity to other types of the same receptor. In this way, it is attempted to justify the change to another opioid, when there is no analgesic effect. An equally important conclusion, supplementing the above-mentioned experiences, may be drawn based on the report by Bolan *et al*., that during the administration of several opioids at the same time, an additive effect was observed [32]. Thus, if opioids act through various classes of opioid receptors, it is justified to assume that the administration of several drugs of the same group in combination may potentiate their action.

A recently published report pertaining to studies on animal models may provide some guidelines facilitating the selection of an opioid. Minami et al. investigated the effectiveness of the analgesic effect of morphine, oxycodone and fentanyl, both in pain caused by bone metastases and in neuropathic pain [33].

The results of the experiment indicate high effectiveness of all the above-mentioned opioids in the pain model for the course of bone metastases. Although during the observations made while successively increasing the administered doses, oxycodone showed a slightly stronger antinociceptive effect, in this case, the differences do not allow the definite preference of this opioid in the indication discussed. The described part of the experiment also throws a new light on the problems of the use of opioids for bone pain. Some practitioners believe that fentanyl is considerably less efficient in this case. The researchers confirmed dose-dependent changes in the sensation of pain by experimental animals in the case of all the drugs examined; therefore, the thesis that in this case fentanyl had no analgesic effect cannot be sustained.

In the report discussed, an interesting compilation is also presented comparing the effect of the drug examined on dose-dependent guarding behaviour, limb-use abnormality and allodynia-like behaviour. The most beneficial action profile was noted in the case of oxycodone, and almost linear relationships were confirmed in all the parameters evaluated, which was not observed for morphine and fentanyl.

In the second part of the experiment, the effect of the drugs examined on neuropathic pain sensation was evaluated. In this case, oxycodone turned out to be the most effective, most strongly inhibiting pain sensations induced by the stimulation of an animal's paw by von Frey's filament, as well as a considerable reduction in guarding behaviour. In the treatment of neuropathic pain, the differences in the effectiveness of action observed between groups treated with oxycodone, morphine and fentanyl were considerably greater than in the bone metastases model.

Based on the above-mentioned studies, it may be concluded that while selecting an opioid, oxycodone should be taken into account as the first-line drug in mixed pain syndromes with a neuropathic component. It should be mentioned, however, that the report discussed concerns an animal model, and therefore should be approached as a guideline for further studies, whereas it will be possible to draw binding conclusions before the confirmation of similar effectiveness in clinical studies.

The stronger effect of oxycodone in neuropathic pain may also be explained by its affinity to κ opioid receptors. During neuropathic pain model experiments, Xu et al. observed an increase in the pronociceptive effect of dynorphins, which are endogenous ligands of this receptor [34]. Therefore, it may be presumed that also in the case of neuropathic pain due to chemotherapy, the specific action of this drug by the activation of κ receptors may result in the reduction of complaints. Similar conclusions were drawn by Nunez while evaluating relatively critically the effectiveness of fentanyl in the treatment of neuropathic pain in the course of cancerous disease, and emphasizing that, in this indication, oxycodone may be considered as the first-line drug [29]. This is also confirmed by the studies by García de Paredes *et al.* presenting the observations of a large group of patients treated with opioids in the same indication [35]. However, due to the fact that this is an observation study, it cannot be considered on the level of evidence-based medicine.

This year, guidelines have been published concerning the treatment of multiple myeloma. This collective work contains guidelines concerning both the principal and symptomatic treatment. In the section devoted to the treatment of pain in the course of this disease, the authors sustain the attitude of the above-quoted researchers, considering oxycodone as the first-line drug in the treatment of neuropathic pain of various aetiology, and thus also in CIPN [25].

Summary

Due to the lack of studies concerning the application of opioids in CIPN, conclusions concerning their effectiveness may be drawn only by analogy.

Based on the literature available concerning model experiments and clinical observations, it may be presumed that opioids are important components of a complex therapy in the case of neuropathic pain, and therefore also effective in the treatment of chemotherapy-induced polyneuropathy.

Affinity of membrane receptors is among the preconditions of the analgesic effect of opioid drugs. The variety of these proteins and their subclasses provides various effectiveness of their ligands, which justifies both opioid rotation and binding.

From among pure opioid receptor agonists, oxycodone showed the strongest analgesic effect in neuropathic pain.

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