

FIRST-LINE PHARMACOTHERAPY OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

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Chemotherapy-induced peripheral neuropathy (CIPN) is a very common adverse event iatrogenically caused by the administration of neurotoxic chemotherapy protocols in oncology patients. Of the chemotherapeutics—oxaliplatin, cisplatin, carboplatin, docetaxel, paclitaxel, vinblastine and vincristine—bortezomib shows the greatest neurotoxicity. Recommendations for the first line of pharmacotherapy of this side effect of chemotherapy are gabapentinoids (pregabalin and gabapentin), antidepressants (amitriptyline, duloxetine, venlafaxine, desvenlafaxine), as well as topical application of lidocaine. Adequate pharmacotherapy of CIPN implies an individualized approach for each patient and compliance with guidelines for recommended first-line pharmacotherapy, first, in the form of monotherapy and later, depending on tolerability and achieved analgesic response, in the form of polytherapy with first-line drugs. If there is no adequate analgesic response to polytherapy with first-line drugs, only then is it necessary to switch to the second line of therapy. Treatment of CIPN leads to an adequate quality of life due to the reduction of the neuropathic component of pain, a reduction in depression and anxiety and the expected completion of the planned chemotherapy cycles, and consequently, a better prognosis of the underlying oncological disease of these patients.

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a very common side effect of chemotherapy, iatrogenically induced in oncology patients. It is known which chemotherapeutic agents cause this side effect, such as platinum derivatives (oxaliplatin, cisplatin, carboplatin) and taxanes (docetaxel, paclitaxel, vinblastine and vincristine, bortezomib) (1).

There are numerous factors that are associated with a higher incidence of CIPN. In a large number of cases, given that it occurs during chemotherapy sessions, it is necessary to reduce the doses of cytostatics in subsequent cycles of therapy and, of course, to implement supportive pharmacotherapy of this side effect (SE) of chemotherapy. Adequate pharmacotherapy of this SE is directly proportional to the completion of the intended chemotherapy sessions in the intended dose regimen and consequently to the survival rate of these patients (2).

In some patients, this SE occurs even after chemotherapy sessions—1 month after completing the first cycle in 68% of patients, 3 months after the end of chemotherapy in 60% of patients, and in 30% of patients after 6 or more months of neurotoxic chemotherapy (3).

Clinical Status and Diagnosis of CIPN

Peripheral neuropathic pain of these patients is characterized by sensations—tingling, pricking, burning, stabbing, cold, electric shock or stabbing sensations that patients state when taking anamnestic data about their neuropathy. This neuropathy is chronic, of significant intensity and responds extremely poorly to the standard analgesic therapy application. The majority of

sufferers also mention other comorbidities such as sleep disorder, anxiety, depression, cognitive disorders, all of which significantly affect the reduction of work ability and quality of life of these patients (4).

In order to be able to diagnose the neuropathy of these patients with certainty, we use some quantitative tools that later serve us to reassess the neuropathy in the controls when we also monitor the therapeutic effect of the prescribed antipain therapy in this group of patients.

In daily clinical practice, multidimensional scales are used to survey patients, and based on the obtained score, we can confidently claim that the patient has a neuropathic component of pain, and during the controls, resurvey and rescore the patients, and thus monitor the effects of the applied pharmacotherapy (5).

One of the most commonly used questionnaires is the painDETECT Questionnaire, which assesses several aspects of pain—nature of pain, pattern of occurrence, strength, spread, and anatomical localization of pain, and based on the obtained score, we can determine the presence of a neuropathic pain component in the surveyed patient. It was translated and validated into the Serbian language. The results obtained with this questionnaire in terms of the neuropathy presence of the surveyed patients include "unlikely" score less than 13 points, "possible" score 13–18 points and "probable" score over 18 points (6). In

addition to this questionnaire, there are other validated and translated questionnaires, such as the DN4 questionnaire (Douleur Neuropathique 4 Questionnaire) (7).

First-line Pharmacotherapy of CIPN

Before starting pharmacotherapy, it is necessary to determine the presence of comorbidities, since depression, anxiety and insomnia can be treated simultaneously with this pharmacotherapy. In addition, the combination of this therapy with cardiology or nephrology therapy can lead to potential interactions and SE, so it is necessary to adjust the dose or revise the choice of drug.

It is necessary to familiarize the patient with the nature of their disease and the detailed pharmacotherapy plan, and to set realistic expectations of the therapy and to familiarize the patient in detail with all aspects of the therapy that will be applied in order to have adequate compliance (8).

Based on the European Federation of Neurological Societies (EFNS) recommendations, the drugs used in the present study for this indication were divided into those that were first therapeutic choice and those that were second therapeutic choice, as shown in Table 1 (9).

Table 1. Recommendations for pharmacotherapy of peripheral neuropathic pain.

First-line pharmacotherapy	pregabalin, gabapentin, amitriptyline, duloxetine, venlafaxine, lidocaine patches
Second-line pharmacotherapy	tramadol, oxycodone, lamotrigine, capsaicin patches

When choosing the drug of the first therapeutic line for the treatment of CIPN, it is necessary to take a good pharmacological anamnesis of the patient in terms of the existence of comorbidities and taking some chronic therapy of the patient, then to familiarize the patient with the expected efficiency and safety of the therapy.

European Federation of Neurological Societies recommendations for the first-line treatment of peripheral neuropathic pain, which includes CIPN, include gabapentinoids, antidepressants and topical analgesics (9).

Gabapentinoids—pregabalin and gabapentin—have found their place in the pharmacotherapy of neuropathy from the group of anticonvulsant drugs. They work with the same mechanism of action, i.e., by binding to the alpha-2-delta subunit of voltage-dependent calcium channels, leading to depolarization, i.e. to a

decrease in the influx of calcium ions into the presynaptic neuron. As a result, the release of excitatory neurotransmitters (glutamate) is reduced, and postsynaptic excitability is reduced. In this way, by reducing sensitization, an analgesic effect is achieved (10). These drugs, in addition to their primary indications, namely adjuvant therapy of partial convulsions in adults with or without secondary generalization and generalized anxiety disorder, have also found their role in the pharmacotherapy of peripheral neuropathic pain, such as CIPN.

The dose titration of these two drugs is different. Namely, pharmacotherapy with any of these drugs should be started in the evening for a few days due to possible dizziness and fainting, and then after a few days, start with the morning dose. It should evaluate and start with the lowest effective dose. The maximum daily dose (MDD) of

pregabalin is 600 mg, and gabapentin is 3600 mg. It is possible to titrate the doses and divide the daily dose of these drugs into 3, when it is necessary for higher dose regimens (11).

Pregabalin has been shown to be effective in all investigated types of neuropathic pain (diabetic polyneuropathy, cancer pain and back pain) with a favorable safety profile and adequate patient adherence. It is structurally similar to the main inhibitory neurotransmitter—gaba-aminobutyric acid (GABA). It is eliminated from the systemic circulation via renal excretion in an unchanged form (< 2% of the dose is detected in the urine in the form of metabolites). Pregabalin clearance is directly proportional to creatinine clearance. Based on this, its use in patients with renal insufficiency is contraindicated. Considering the route of elimination of this drug as well as its biotransformation, drug-drug interactions are very rare because it is excreted unchanged by renal excretion, so it is possible to combine it with other drugs that act on the CNS, e.g. opioid analgesics in the treatment of mixed malignant pain syndrome. The initial dose is usually 150 mg divided into two equal daily doses. Given that it has been proven that pregabalin has a dose-dependent effect, i.e. its effectiveness increases directly proportionally with the applied dose, in cases of inadequate analgesic response, it is advised to increase the dose to 300 mg during one week of therapy. The favorable pharmacokinetic profile of pregabalin is reflected in the rapid reaching of the maximum drug level in plasma (0.7–1.3 h), good tolerability, bioavailability (90%), short elimination half-life (4.6–6.8 h), absence of drug-drug interactions and hepatic side effects (12).

Pharmacotherapy with gabapentin usually starts with a dose of 300 mg per day with gradual titration as with pregabalin, and the MDD is 3600 mg. As with pregabalin, with larger doses, it is possible to divide the entire dose into three equal doses, i.e., that in addition to the morning and evening doses, the midday dose of the drug should also be introduced, given that its elimination half-life is 5–7 hours. The path of biotransformation and excretion of gabapentin is the same as that of pregabalin, and renal insufficiency is also a contraindication for the use of this drug. The most common SEs that occur during the use of these two drugs are dizziness, drowsiness, headache, dry mouth, appearance of peripheral edema and weight gain. They are usually mild to moderate in intensity and disappear when the dose is reduced (13).

Antidepressants also occupy their important place in CIPN pharmacotherapy. Today, it is avoided by the use of tricyclic antidepressants (TCAs). From this group of drugs, the only one that has found its place for these therapeutic purposes is amitriptyline. Tricyclic antidepressants achieve their analgesic effect completely independently of their antidepressant effect. They can have an antidepressant and analgesic effect equally well. The analgesic effect is achieved by inhibiting serotonin uptake into nerve endings,

blocking sodium channels, modulating cholinergic and histaminergic transmission and reducing central sensitization. Pharmacotherapy with amitriptyline is started gradually, usually 10 mg or up to 25 mg in the evening with a gradual titration of the dose on a weekly basis to a maximum effective dose of 75–150 mg per day. At the same time, amitriptyline improves sleep and reduces anxiety in these patients. A contraindication for the use of TCAs and the reason why many clinicians avoid prescribing them to their patients is cardiotoxicity, especially in patients with conduction disorders and arrhythmias. Among the SEs, anticholinergic effects that can be quite pronounced (confusion, urine retention, constipation, orthostatic hypotension), prolongation of the QT interval, and excessive sedation are significant (14).

Today, in daily clinical work, most often for the treatment of peripheral neuropathies and also CIPN, antidepressants are drugs from the group of selective serotonin and noradrenaline reuptake inhibitors (SNRIs), namely duloxetine and venlafaxine. By inhibiting the uptake of serotonin and noradrenaline in the descending pathways for pain, they achieve their analgesic effect in addition to the basic antidepressant effect. Their advantage over TCAs is a better safety profile in terms of very minor and mild SEs, and they can be used more safely in high-risk populations such as the elderly and co-medicated with other drugs.

Duloxetine has its primary indication area, such as major depression, obsessive-compulsive disorder, generalized anxiety disorder. In addition to these psychiatric indications, today it is successfully used in the pharmacotherapy of neuropathic pain and fibromyalgia. Its effectiveness has been proven in the treatment of neuropathic pain caused by chemotherapeutic agents, diabetic polyneuropathy, radiculopathy, and neuropathy in multiple sclerosis. Recommended doses of duloxetine are 60–120 mg per day. The recommendation for the use of antidepressants is to take the daily dose in the morning due to the energizing effect. The advantage of duloxetine over venlafaxine is that it is safer in cardiovascular patients, while SE patients can expect nausea, vomiting, increase in liver enzymes, and fainting (15).

Venlafaxine is also a drug from the SNRI group that is used in the pharmacotherapy of major depression, panic disorders, social phobias and generalized anxiety disorder. This drug can be used in CIPN with initial doses of 37.5–75 mg per day with gradual titration to a therapeutically effective dose of 150–225 mg per day, and the maximum daily dose is 375 mg per day. In lower doses, up to 100 mg per day, it inhibits the reuptake of serotonin, while the reuptake of noradrenaline increases in the range of 100–375 mg per day. It has been proven to be the most effective in the treatment of diabetic polyneuropathy and postherpetic neuralgia. The most common SEs of using this drug are arterial hypertension, hyponatremia and disorders of the gastrointestinal tract, as well as sexual dysfunctions (16).

Today, in addition to venlafaxine, desvenlafaxine is also available as an adequate therapeutic substitute with a better safety profile than venlafaxine. Desvenlafaxine is an active metabolite of venlafaxine, belonging to the SNRI group, which is used in the treatment of major depressive disorder, as well as in the treatment of certain forms of chronic pain. The usual starting dose is 50 mg, which can be increased up to 200 mg per day, depending on the patient's individual needs and response to therapy. It is used in the treatment of peripheral neuropathic pain, including pain associated with diabetic polyneuropathy, fibromyalgia, and chronic pain in patients with depression, as well as in CIPN (17). The mechanism of action in pain therapy is similar to its antidepressant effect, because it increases the concentration of noradrenaline and serotonin in the central nervous system, which contributes to the analgesic effect. The most common SEs are nausea, diarrhea, dry mouth and dizziness, which mostly occur during the introduction of therapy and are transient. Compared to venlafaxine, it has more stable pharmacokinetics, a lower risk of hypertension onset and easier dosing without the need for titration. Additionally, it undergoes minimal first-pass metabolism through the liver, which reduces the possibility of interaction with other drugs (18).

Topical analgesics, in first-line therapy, include lidocaine patches. The advantage of topical application of lidocaine to painful areas is that there is no systemic resorption and therefore no possible systemic therapy SEs. The only SE is local mild skin irritation at the application site. Lidocaine is used in the form of 5% lidocaine patches (700 mg lidocaine). Up to 4 patches per day can be applied with a therapeutic effect that can be maintained for 18 to 24 hours. Side effects of systemic resorption is manifested in the form of central nervous system (CNS) excitation (trembling, shaking, convulsions) and/or CNS depression (respiratory depression, respiratory arrest), cardiovascular manifestations, such as myocardial depression, atrioventricular block and vasodilatation leading to hypotension (19).

Lidocaine acts by reducing neuronal excitability at the level of sodium channels and by inhibiting the propagation of action potentials, and by reducing sodium permeability depolarization as a manifestation of nerve conduction is prevented. Lidocaine first shows its effect on smaller diameter fibers (A δ and C fibers), and then on motor axons. It is effective as an adjunct to oral pharmacotherapy of peripheral neuropathies. Caution is required in patients who are on co-medication with antiarrhythmics (mexiletine) and in those with impaired hepatic function (20).

EMLA cream contains 20% pure lidocaine and an 80% lidocaine/prilocaine mixture. There is evidence of the effectiveness of this topical agent in relieving pain in peripheral neuropathies, especially during the first 2 hours after application (21).

Dexamethasone and betamethasone are long-acting corticosteroids that can be co-

administered in patients with chronic peripheral neuropathy. These drugs can be prescribed with a limit of use of up to 15 days and a gradual de-escalation of the dose within that time period due to possible systemic SEs. Use longer than 3 weeks can lead to metabolic side effects such as: hyperglycemia, iatrogenic Cushing's syndrome, immunosuppression and greater susceptibility to infections, osteoporosis and the occurrence of pathological fractures. They achieve their antipain effect, especially in the acute phase of painful neuropathies, with their strong anti-inflammatory and antiedematous effect. Thanks to the long half-life of elimination (36–54 hours), dosing is very comfortable. Dexamethasone can be administered both parenterally and orally, while betamethasone is administered as depot formulations on a weekly basis (22, 23).

Second-line therapy is applied only if all therapeutic possibilities of monotherapy or combined therapy with first-line drugs have been exhausted. Medicines of this category mainly suppress the nociceptive component of pain, and do not have an adequate analgesic effect on the neuropathic component, and therefore belong to the alternative therapy of peripheral neuropathies and thus CINP (9).

If the introduction of first-line pharmacotherapy for the treatment of peripheral neuropathic pain, which includes CIPN, achieves a reduction in pain with an intensity equal to or less than 3 on the pain intensity scale, with tolerable SE, it is advised to continue the started pharmacotherapy due to an adequate analgesic response. If, after the introduction of the therapy, partial pain control is achieved, i.e. pain intensity is still greater than 4 on the scale of pain intensity, it is necessary to add another drug from the group of drugs of the first therapeutic choice. If the pain control is inadequate to the original therapy, with pain intensity reduced by less than 30% and in addition to taking the optimal dose of the drug of the first therapeutic choice for a long enough time, it is advised to stop the first-introduced drug and switch to an alternative drug of the first therapeutic choice (24). In daily clinical practice, the fact that chronic neuropathic pain, such as CIPN, cannot be cured by monotherapy is very often encountered, so it is necessary to introduce rational polytherapy, which involves combining drugs with different mechanisms of action, which should lead to an adequate analgesic response through a synergistic effect. The combination of one of the gabapentinoids with opioids/antidepressants/topical analgesics showed the greatest effectiveness. With such combinations, it is always necessary to keep in mind the safety and tolerance of the prescribed polytherapy and not just the efficiency. When combining these drugs, it is possible to have additive SE, drug-drug interaction, which leads to a decrease in patient compliance. If monotherapy with drugs of first choice or their combination within polytherapy does not lead to adequate relief of peripheral neuropathy, it is recommended to introduce drugs of second therapeutic choice and

non-pharmacological methods of treatment within the framework of a multidisciplinary assessment of the patient (25).

Conclusion

Chemotherapy-induced peripheral neuropathy is a very common adverse event iatrogenically caused by the administration of neurotoxic chemotherapy protocols in oncology patients. This SE of chemotherapy should not be ignored, but it is necessary to implement adequate pharmacotherapy respecting the individualized approach to each patient and the guidelines for recommended first- and second-line pharmacotherapy, first in the form of monotherapy and later, depending on tolerability and the achieved analgesic response, in the form of polytherapy with first-line drugs. If there is no adequate analgesic response to polytherapy with

first-line drugs, only then is it necessary to switch to the second line of therapy. Adequate treatment of this neuropathy enables oncology patients to have an adequate quality of life due to the reduction of the neuropathic pain component, a reduction in depression and anxiety, and also the completion of planned chemotherapy cycles that lead to a better prognosis of the underlying oncological disease, which is why CIPN pharmacotherapy is extremely important.

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PRVA LINIJA FARMAKOTERAPIJE PERIFERNE NEUROPATIJE INDUKOVANE HEMIOTERAPIJOM

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Periferna neuropatija indukovana hemioterapijom (engl. *chemotherapy-induced peripheral neuropathy* – CIPN) predstavlja veoma čestu neželjenu pojavu, koja je jatrogeno izazvana sprovođenjem neurotoksičnih hemioterapijskih protokola na onkološkim pacijentima. Najveću neurotoksičnost među hemioterapeuticima pokazuju oksaliplatin, cisplatin, karboplatin, docetaksel, paklitaksel, vinblastin i vinkristin, boretzomib. Preporučuje se da se za prvu liniju farmakoterapije ovog neželjenog efekta hemioterapije koriste gabapentionoidi (pregabalin i gabapentin) i antidepresivi (amitriptilin, duloksetin, venlafaksin, desvenlafaksin). Takođe, preporučuje se topikalna primena lidokaina. Adekvatna farmakoterapija CIPN-a podrazumeva individualizovani pristup pacijentu i poštovanje smernica za preporučenu farmakoterapiju prve linije, najpre korišćenjem jednog leka, a potom, u zavisnosti od tolerabilnosti i postignutog analgetskog odgovora, i korišćenjem većeg broja lekova iz prve linije farmakoterapije. Treba preći na drugu liniju terapije jedino ako nema adekvatnog analgetskog odgovora na politerapiju lekovima iz prve linije. Zbrinjavanje CIPN-a omogućava bolji kvalitet života, budući da dolazi do kupiranja neuropatske komponente bola, smanjenja stepena depresivnosti i anksioznosti i predviđenog završetka planiranih hemioterapijskih ciklusa; samim tim, prognoza lečenja osnovnog onkološkog oboljenja ovih pacijenata postaje bolja.

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Ključne reči: hemioterapija, periferna neuropatija, farmakoterapija

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