

The incidence of chemotherapy-induced peripheral neuropathy (CIPN) in the population of cancer patients is estimated at 3–7% in cytostatic monotherapy and as high as 38% in the case of polytherapy. While testing drugs that may reduce the damage to the peripheral nervous system, particular attention should be paid to their protective action against the severe and painful complication in the patient. Another aspect, perhaps a more important one, is the confidence that application of preventive drugs will not exert a significant impact on progression of the neoplastic disease or the effectiveness of the causal treatment. Many drugs have been tested for prevention of CIPN; however, none of them have thus far been irrefutably proven to possess preventive properties. No guidelines on chemotherapy-induced peripheral neuropathy preventive action have been established, either. This article is an attempt to present reports from the available literature about the possibilities of prevention of CIPN.

Key words: chemotherapy-induced peripheral neuropathy, neuropathic pain, side effects, prevention.

Chemotherapy-induced peripheral neuropathy. Part II. Prevention

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Pain symptoms experienced by patients with a cancer disease usually have a mixed nature, as nociceptive and visceral pain is accompanied by a neuropathic component related to the damage to the peripheral nervous system (PNS). Management of neuropathic pain is extremely difficult; therefore, proper diagnosis and implementation of appropriate treatment contribute to alleviation of the symptoms [1–3].

Damage to a nerve, an anatomical structure, usually produces pain symptoms through external pressure (tumour growth; presence of bone material in pathological fracture; rarely, metastases to nerves). From a neuropathological point of view, the sequence of events includes two steps. The first one is characterized by occurrence of neurogenic pain (caused by nerve compression) which, when prolonged, results in damage to the nervous fibres and, consequently, neuropathic pain.

Another form of neuropathic pain is chemotherapy-induced peripheral neuropathy (CIPN). In this case, axonal damage is induced by the action of cytostatics and therefore the syndrome is classified as toxic neuropathy [4].

The incidence of CIPN in the population of cancer patients is estimated at 1–12% [5], although recent reports allow a presumption that the prevalence of the phenomenon is increasing [6]. Slightly different conclusions can be drawn from the paper by Cavaletti and Zanna [7], who estimate the incidence at 3–7% in the case of cytostatic monotherapy and as much as 38% in polytherapy.

Chemotherapy-induced peripheral neuropathy cannot be regarded as a homogeneous syndrome, given the great variety of cytostatic drugs exhibiting different modes of damaging the PNS. Symptomatology and localization of the symptoms are the only common factors (these issues were addressed in a previous paper [8]). No safe and effective model of management of a CIPN patient has been developed so far. The authors of proposed algorithms concurrently emphasize that evidence-based medicine provides no convincing proof; hence the possibilities of implementation of these algorithms are limited [9].

Initiation of chemotherapy is accompanied by the doctor's awareness that occurrence of the discussed syndrome is highly probable and may even lead to discontinuation of the causal treatment. This paper is an attempt to present reports from current literature concerning the possibilities of prevention of CIPN.

Methods of chemotherapy-induced peripheral neuropathy prevention

While testing drugs that could possibly decrease the damage to the PNS, attention should be paid to their protective action against severe and painful complications in the patient. Another, perhaps more important, aspect is the confidence that the application of preventive drugs will not exert a significant impact on the progression of the neoplastic disease or on the effectiveness of the causal treatment. Model tests of numerous substances yielded promising results; yet, in clinical trials, either their effectiveness was not proven or they exhibited pro-carcinogenic activity. The results of investigations

Table 1. List of drugs tested for their effectiveness in CIPN prevention

Tested drug	Cytostatic drug	Limitations	Conclusions	
			PREV (+/-)	CHEM (+/-)
Ca ²⁺ , Mg ²⁺ ions	oxaliplatin		+	
vit. E 600 mg	cisplatin		+	+
amifostine	cisplatin, paclitaxel		+/-	+/-
glutathione	cisplatin	(small group)	+	+
glutamine	paclitaxel		+	?
N-acetylcysteine	oxaliplatin		+	?
acetyl-L-carnitine	cisplatin, paclitaxel	(no placebo, small group)	+	?
carbamazepine	oxaliplatin		-	?
oxcarbazepine	oxaliplatin	(no placebo, small group)	+	?
venlafaxine	oxaliplatin	(no placebo, small group)	+	?

PREV – effectiveness of prevention, CHEM – impact of the drug on chemotherapeutic activity, (+) – positive, (-) – negative

of some methods of PNS damage prevention will be discussed below; Table 1 contains the cumulative data.

Calcium and magnesium ions

Gamelin *et al.* presented encouraging results of a study aiming at prevention of PNS damage by application of magnesium and calcium ions during oxaliplatin therapy [10]. The positive results of these observations were even more interesting since this management would not involve high expenses or require specialized equipment. Hochster *et al.* [11] aimed to verify this hypothesis, yet the investigation had to be discontinued due to accelerated neoplastic disease progression. Although the positive action of magnesium and calcium in CIPN prevention was confirmed, the ions were concurrently reported to reduce the anti-tumour activity of oxaliplatin. This phenomenon implies that application of ions of some metals prevents both neuro- and cytotoxicity [12]. Unfortunately, the current knowledge of this activity does not promote such management due to the risk of reduced effectiveness of chemotherapy.

Vitamin E

In 2003, Pace *et al.* published the results of investigations employing the anti-oxidative activity of vitamin E in the dose of 300 mg/day [13]. An important observation was the lack of interaction of vitamin E with the anti-tumour action of cisplatin. The studies were repeated by Argyriou *et al.* [14–16], who reported very positive effects of application of vitamin E in the dose of 600 mg/day both in combination with cisplatin and paclitaxel therapies. Therefore, supplementation with vitamin E may be regarded as a method of CIPN prevention, although further investigations are advisable [12, 17].

Amifostine

Amifostine is an organic thiophosphate compound, whose anti-oxidative activity is based on scavenging free rad-

icals. The first attempts to use this compound for prevention of CIPN demonstrated that the pathology of the peripheral nervous system occurred at a higher cumulative dose of cisplatin with no concurrent side effects [18]. Subsequent tests performed to determine the effectiveness of this procedure in patients treated with cisplatin combined with paclitaxel [19] and cisplatin with cyclophosphamide [20] did not reveal any positive effect. In turn, the study conducted by Kemp *et al.* demonstrated substantial limitations in the use of this compound due to the frequent events of hypotonia during amifostine infusion [20].

Glutathione

The preventive effect of glutathione involves reduction of the cisplatin concentration in spinal ganglion cells and an impact on cisplatin-induced protein p53 [21, 22]. However, there is a risk that glutathione will reduce the anti-tumour activity due to increased renal excretion of cisplatin. Although randomized placebo-controlled trials have confirmed the effectiveness of CIPN prevention without a substantial impact on the basic treatment [23], positive results were obtained from a small number of patients tested; therefore this procedure cannot be fully recommended.

Glutamine

Glutamine is a specific endogenous amino acid which should be regarded as an exogenous amino acid in cell damage. Its role in CIPN prevention involves inhibition of oxidative stress [24]. It was reported that this amino acid may have an effect on production of the nerve growth factor (NGF), whose presence may be an important inducer of CIPN [25, 26]. Supplementation with non-essential amino acids may be related to the risk of their impact on the development of all fast-dividing cells; therefore, it is possible (although not proved clinically) that glutamine may induce tumour expansion. Clinical trials have proved the efficacy of this amino acid in prevention of CIPN in patients treated with paclitaxel; yet,

the fear of reduced effectiveness of its anticancer activity limits its implementation of this procedure [17, 24].

N-acetylcysteine

N-acetylcysteine plays a role in protecting the cells of the nervous system by increasing glutathione levels in the spinal ganglion cells. Only one study has reported the positive effect of this preventive procedure in patients treated with oxaliplatin [27]; the insufficient number of patients tested does not allow realistic assessment of the safety of application of the drug.

Acetyl-L-carnitine

The preventive mechanism of this compound is not known, but it was found that it both exerts an effect on regeneration of damaged nerve fibres and reduces pain impulses in fibres A and C [28–30]. Non-placebo-controlled trials performed on a small group of patients treated with paclitaxel or cisplatin have demonstrated positive effects [31]; nevertheless, they are insufficient to recommend the drug for clinical use.

Human recombinant interleukin

Cytokines may play a substantial role in induction of the damage to the PNS. Model studies demonstrated a preventive action of interleukin 6 in CIPN induced by paclitaxel, cisplatin, and vincristine [32]. Further clinical trials did not confirm the assumed preventive activity, as there were no significant differences between the patients receiving therapy and those receiving placebo [33–35].

Antiepileptic drugs

Impairment of sodium channel function is one of the probable mechanisms responsible for neuronal damage accompanying oxaliplatin therapy [36–38]. Since carbamazepine inhibits the activity of these channels, attempts were made to apply the drug to prevent CIPN. Unfortunately, no differences were found between the test and placebo groups [36].

Oxcarbazepine is a more recent anti-epileptic drug that affects both sodium and calcium channels. Although trials performed to assess its preventive action during oxaliplatin therapy yielded a positive outcome, they were non-placebo-controlled and involved a small group of patients. Therefore, they should be regarded as pilot studies providing no recommendations for using the drug in clinical practice [36]. Conclusions from the reports of the use of venlafaxine reveal similar limitations [39].

The effectiveness in prevention of CIPN has been tested in many drugs with no conclusive outcome. No guidelines for preventive procedures applied during chemotherapy have been established, either. Some hope can be attached to the few studies reporting attempts to implement CIPN management algorithms [40], which may alter the current approach to prevention and management of this severe pain syndrome. There is a need for further prospective studies evaluating the effectiveness of CIPN prevention and its safety associated with absence of any impact on the causal treatment of cancer.

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