

Chemotherapy-induced peripheral neuropathy (CIPN) is a toxic neuropathy, a syndrome consisting of highly distressing symptoms of various degrees of severity. It includes numbness of distal extremities, long-term touch, heat, and cold dysaesthesia and, in more severe cases, motor impairment affecting daily functioning. Each form of the syndrome may be accompanied by symptoms of neuropathic stinging, burning, and tingling pain. In the case of most chemotherapeutic agents, the incidence and severity of CIPN are dependent on the cumulative dose of the drug. The syndrome described is caused by damage to the axons and/or cells of the peripheral nervous system.

Chemotherapeutic agents have distinct mechanisms of action in both neoplastic tissue and the peripheral nervous system; therefore, CIPN should not be regarded as a homogeneous disease entity. The present article is an attempt to systematize the knowledge about the toxic effects of chemotherapy on the peripheral nervous system.

**Key words:** chemotherapy-induced polyneuropathy, neuropathic pain, side effects, pathophysiology.

# Chemotherapy-induced polyneuropathy. Part I. Pathophysiology

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Treatment of patients with neoplastic disease is frequently associated with chemotherapy-induced peripheral neuropathy (CIPN), which is a syndrome consisting of highly distressing symptoms of varied degrees of severity. Most commonly, it begins with numbness of distal extremities, and may progress to long-term touch, heat, and cold dysaesthesias and severe motor impairment affecting daily functioning. The disorders described are commonly accompanied by stinging, burning, tingling or electric shock-like neuropathic pain.

Effective anti-tumour therapy improves patients' survival, thereby increasing the number of patients struggling with problems resulting from the prior treatment. Therefore, the problem of painful peripheral neuropathy may be assumed to persist. It should be borne in mind that other forms of anti-tumour therapy may also cause nervous system damage [1].

Currently, no methods are available that are proven and based on evidence-based medicine for management of these symptoms; it is however optimistic that the number of publications on their pathomechanism, prevention, and treatment is constantly increasing. In the case of most chemotherapeutic agents, CIPN severity depends on the cumulative dose of the drug administered; therefore limiting treatment is the most common method for protecting patients against such symptoms [2-4]. The relevance of such a therapy scheme has been confirmed by model studies [5]. This certainly cannot be the most optimal treatment method, since it involves choosing between its efficacy and toxicity; still, it seems to be the safest option given the current state of knowledge [6].

Chemotherapeutic drugs are particularly active in organs whose cells undergo frequent divisions; therefore, the side effects of cytostatics are mainly manifested in the gastrointestinal tract, skin, and hematopoietic system.

New chemotherapeutic agents display higher selectivity; hence, as might at least be assumed, they should be less toxic to healthy tissues. Unfortunately, the endings of nerve fibres and supporting cells of the peripheral nervous system are paradoxically very sensitive to this type of medication. Agents acting through disruption of the spindle microtubules impair the microtubule-dependent axonal transport as well. Toxic effects of chemotherapeutic agents on the peripheral nervous system may thus be manifested [7].

The effect exerted by a combination of various chemotherapeutic agents on the incidence and course of CIPN is not known. In most cases, they are administered in multi-drug schemes, while monotherapy is relatively rarely employed. It is probable that their additive or synergistic activity against neoplastic cells may affect the cells of the peripheral nervous system as well [8, 9]. To date, no prospective studies addressing the problem have been conducted. Similarly, there are no clear algorithms for the diagnosis, prophylaxis, and treatment of the syndrome [10, 11].

When CIPN is diagnosed in a patient who was pre-treated with other drugs, it is very difficult to identify the direct cause of the syndrome. Patients are often subjected to different modes of therapy that may delay the symptoms. For instance, dysaesthesia occurs relatively late (even a few months after cis-

platin therapy); therefore, it is often ascribed to drug toxicity or regarded as aggravation of symptoms [12], while actually it may be an effect of a previously discontinued treatment.

Examination of nerve conduction and electromyography do not provide precise information about disease occurrence and severity. This is related to the fact that these examinations are focused on the pathology of larger nerve fibres or the neuromuscular junction, while the syndrome described is caused by changes within the thin peripheral bands. Therefore, the accuracy of these studies is insufficient to evaluate chemotherapy-induced changes. Great expectations are attached to examination of evoked potentials, yet even so accurate a diagnosis should be supplemented by peripheral nerve biopsy [13].

Any form of damage to the peripheral nervous system, even if it was diagnosed many years before, is a predisposing factor. Signs of monoclonal gammopathy may often be the first symptoms of neuropathy in the course of other disease entities, e.g. multiple myeloma [14]. The primary cause of the disease does not seem important, as such regularity has been found in both hereditary and inflammatory neuropathy [15-18]. Similarly unimportant is the length of the symptom-free period before chemotherapy [7]. The mechanism described has not been found in patients previously suffering from diabetic polyneuropathy [19] and the available literature does not provide a clear explanation of the absence of increased CIPN incidence in such cases.

### Neurotoxicity of particular drug groups

The information about the mechanisms of action of the drugs presents the aspect of induction of damage to the peripheral nervous system, rather than their anti-cancer activity.

#### Platinum derivatives

The concentration of platinum derivatives in peripheral nerves is comparable to their concentration in the tumour, but significantly lower than that in the brain [20-22]. This is associated with their easy permeation through the capillary network and impeded delivery to the central nervous system [23-25]. Model experiments have revealed a strong affinity of both cisplatin and oxaliplatin to the deoxyribonucleic acid (DNA) of spinal ganglion cells [26, 27]. Strong binding of the drug to the DNA structures is an important mechanism of anticancer action, although it is the cause of apoptosis of the nervous system cells [28]. In turn, binding of platinum derivatives to mitochondrial DNA is regarded as a probable cause of neuronal death [29]. According to some authors, this mechanism is frequently recognized in patients with Lhermitte's sign [7, 30].

In this group of drugs, **cisplatin** has been used the longest; the frequency of its adverse effects is clearly dependent on the cumulative dose [31-33]. Damage to the peripheral nervous system is usually diagnosed at the cumulative dose of 400-500 mg/m<sup>2</sup>, i.e. after three to six months of treatment [22, 34, 35]. The clinical symptoms primarily begin with the hand-foot syndrome accompanied by paraesthesias and dysaesthesias. Sensory ataxia may sometimes

occur. The question why the side effects sometimes appear only three to six weeks after discontinuation of cytostatic therapy [36] and may progress gradually over many months [37] has not been elucidated yet. Symptoms from the autonomic nervous system are less common and include fatigue, cardiac arrhythmias, and impotence [7, 38].

The frequency and severity of adverse effects of oxaliplatin have been shown to be dependent on the drug dose [39, 40], although the phenomenon is not as severe as in the case of cisplatin. A large proportion of patients (60-80%) feel unpleasant cold-induced paraesthesia especially around the throat, on the whole face or around the mouth, and on the hands. It is described as a burning or pinching sensation caused by contact with a cold surface or cold liquids. It usually appears during the second or third cycle, persists for approximately 30-60 minutes, and has a transient character. About 20-30% of patients suffer from similar symptoms when treated with cisplatin [39, 41, 42]. It was found that this phenomenon was directly related to the cumulative dose [43, 44].

Carboplatin displays significantly lower neurotoxicity [33], although in higher doses it can induce symptoms similar to those produced by cisplatin. A more important fact in the case of the side effects of this drug is that it is frequently used in combination with paclitaxel; neurotoxicity may occur in 20% of patients receiving such treatment [45].

Differential diagnosis is focused mainly on paraneoplastic ganglionopathy [46-48]. Unfortunately, laboratory tests detecting presence of syndrome-specific antibodies, cerebrospinal fluid examination, or nerve biopsy do not ensure conclusive results. It is still necessary to rely on differences in the clinical course. The paraneoplastic syndrome yields asymmetrical signs in the upper extremities and face, whereas CIPN is often symmetrical, more commonly affects the lower extremities, and the facial symptoms are transient. Neuropathy is a frequent phenomenon (about 30% of patients), while the paraneoplastic syndrome occurs relatively seldom.

When chemotherapy is discontinued due to the onset of peripheral neuropathy, it is possible that the syndrome will further develop. The fact that the active substance in the drug is removed from the body within 96 hours after cessation of drug administration seems irrelevant, as changes in the nervous system have been initiated, and currently there are no methods for protecting the patient against progress of the changes. This phenomenon is called "casting". Although its existence has been acknowledged, neither its mechanism nor inhibition methods are known [6, 7, 49].

#### Inhibitors of the spindle apparatus

The mechanism of anti-tumour action of these drugs involves inhibition of formation of mitotic spindle microtubules. This reduces the rate of cell divisions, thereby inhibiting tumour growth. Microtubules fulfil an important role in axonal transport that ensures proper functioning of nerve fibres. Inhibition of this mechanism leads to functional and structural abnormalities of the axon and, consequently, to its death. The damage mechanism specifically affects thin non-myelinated nerve fibres [50]. A correlation has been found between the level of exposure to toxic agents and incidence of nerve

ending damage; hence, longer axons exhibit greater susceptibility: the longer the axon, the greater the risk of CIPN occurrence. This explains the typical course of neuropathy that starts in the distal part of the lower extremities and gradually progresses onto the upper parts. Symptoms in the upper extremities appear in the subsequent stage. Neuropathy induced by all drugs of this group has sensory, motor, and autonomous nature. Since the mechanism of its appearance is typically peripheral (without cell damage), functioning of the nervous system can be successfully restored in most cases [7].

**Vinca alkaloids** exhibit low ability to permeate the blood-brain barrier [51-53]; this restrains the damage to the peripheral parts of the nervous system with no distinct toxicity to the nerve cell [54-56].

Neuropathy induced by this group of drugs is dose-dependent. Chemotherapy-induced peripheral neuropathy induced by vincristine and vindesine is more severe, whereas vinblastine and vinorelbine are characterized by lower neurotoxicity. A higher risk of neurological damage is associated with administration of vinorelbine in patients pre-treated with paclitaxel [57]. Symptoms usually begin within the first three months after therapy initiation. The first symptoms usually include paraesthesia and pain of the feet and hands accompanied by gradually increasing hyperalgesia. Decreased muscle power, particularly in the wrist and thenar, is a common symptom. There have been reports of cases of mononeuropathy of the lower extremities, cranial nerve damage resulting in diplopia, hearing disorders, and vocal fold palsy [58-61]. The risk of weakened peristalsis accompanied by adynamic ileus is a life-threatening complication [62]. Bladder atony, impotence, orthostatic hypotension and cardiac arrhythmias are relatively common [63, 64]. A rare complication, i.e. progressive motor neuropathy leading to quadriplegia, has also been reported [65]. Serious complications – severe symptoms of neuropathy – have been described in cases where hereditary or inflammatory neuropathy has been diagnosed previously [15, 17, 18], as mentioned at the beginning of the paper.

Besides CIPN, acute inflammatory demyelinating polyradiculoneuropathy (AIDP) as well as infiltration of nerves or nerve roots should also be taken into account in the differential diagnosis.

A characteristic feature of peripheral neuropathy is symmetrical and distal emergence of symptoms accompanied by slow aggravation of symptoms. Acute inflammatory demyelinating polyradiculoneuropathy occurs more proximally and is associated with an asymmetrical reduction in muscle power in the area of affected root innervation; symptom development exhibits a higher rate. Nerve root infiltration has to be taken into account in cases where asymmetrical pain is the predominant symptom. In turn, infiltration of peripheral nerves should be suspected in cases of asymmetrical mononeuropathies. Cerebrospinal fluid examinations and diagnostic imaging are useful tools [66].

No algorithms of treatment or prevention of peripheral neuropathy caused by vinca alkaloids have been devised to date. Currently, the only way to mitigate the risk of nerve damage is to reduce the chemotherapy dose, although further development of the syndrome cannot be fully excluded [12].

In mild cases, recovery may be expected within a few months; in more severe cases, it may be substantially prolonged. It should be taken into account that the symptoms may be chronic and persist for years. In the case of neuropathy accompanied by immense pain, methods of neuropathic pain treatment should be employed [67-70].

Like vinca alkaloids, **taxanes** interfere with mitotic spindle microtubules, but unlike the former, the latter induce excessive stabilization of these structures, thereby preventing normal cell division. Their effect on functioning of the peripheral nervous system is similar to that exerted by vincristine. Excessive stabilization of microtubules required for normal axonal transport results in substantial disturbances and, consequently, considerable damage to their peripheral parts [71]. The clinical effects are not as serious as in the case of the drugs described previously.

Dose-dependent sensory symptoms appear to be less severe than the symptoms induced by the other drugs in this group [72]. These include paraesthesias, sensory disturbances, and foot and hand dysaesthesias. Activities **requiring** manual precision, such as writing or fastening buttons, may often pose problems. Tendon reflexes and muscle strength may be weakened, although these are rather rare cases. Docetaxel causes a more severe CIPN course than paclitaxel [73]. Since taxanes are often combined with other drugs exhibiting a high potential for damaging the peripheral nervous system, it is difficult to assess which therapy component plays a key role in the pathology development, as there have been no studies addressing this issue.

The differential diagnosis is similar to that used in the case of vinca alkaloids, and the symptoms usually improve within several weeks after discontinuation of treatment. Reduced drug doses together with increased duration of treatment decrease the incidence of complications.

Complications induced by **podophyllotoxin** derivatives include ataxia, encephalopathy, and myelopathy [74]; however, there is no evidence that therapy with drugs from this group evokes CIPN. Although epothilone neurotoxicity has been reported [75], it may be ascribed to the toxicity of Cremophor used to increase the water solubility of these drugs [76].

**Bortezomib** was introduced in treatment of multiple myeloma due to its unique mechanism of action through proteasome inhibition. The pathophysiology and treatment of bortezomid- and thalidomide-induced CIPN was described in detail by Bilińska *et al.* [77].

### Alkylating agents

**Cyclophosphamide** exerts no significant effect on the emergence of CIPN, and the estimated incidence of this syndrome induced by ifosfamide is ca. 8% upon administration of elevated doses only [78]. The slow onset of symptoms is followed by aggravation thereof and emergence of paraesthesias and foot pain. Tendon reflexes are weakened but excessive leg fatigability is rare. After treatment discontinuation, the symptoms disappear slowly (up to several years), but there is never full recovery.

**Procarbazine** used in chemotherapy of brain tumours and in onco-haematology rarely causes severe neuropathy; yet, cases of myalgia are more common [79].

Intrathecal administration of thiotepa may lead to myelopathy [80] or motor neuropathy [81]. High intravenous doses may induce encephalopathy [82].

### Antibiotics

The group of anti-tumour antibiotics consists of many drugs widely used in chemotherapy. Damage to dorsal root ganglion cells induced by doxorubicin has been reported from model experiments [83, 84]; yet, no severe peripheral neuropathy caused by this group of drugs has been described. Cardiotoxicity of doxorubicin is most pronounced, whereas neurotoxicity is observed upon application of the drug in combination with vincristine or thalidomide [7]; therefore, it can be treated as the effect of the other components of the combination therapy.

### Antimetabolites

The mechanism of action of this group of drugs involves inhibition of synthesis of certain metabolites required for normal synthesis of ribonucleic acid (RNA) and DNA. Neuropathy diagnosed upon application of these drugs often has a central rather than peripheral form. Since only single cases of CIPN have been reported and no research has been conducted on larger material, it can be concluded that this is not a common complication after treatment with antimetabolites.

Intrathecal administration of **methotrexate** may induce neurotoxicity of this drug, although peripheral neuropathy is rare. In the literature, lumbosacral plexopathy has been reported in both children [85] and adults [86]. It cannot be excluded that it is caused by a malignant process in the central nervous system or concomitant use of other drugs, particularly vincristine [87-91].

Cytosine arabinoside (Ara-C) in monotherapy and in combination with fludarabine may cause myelopathy or encephalopathy [92]. Peripheral neuropathy is as rare in this case as in application of other drugs of this group [93, 94]. Reports on this issue primarily contain descriptions of cases that cannot be directly compared to clinical practice. Ara-C is still recommended for meningioma treatment and the risk of peripheral neuropathy is considered low.

In 10% of patients, **gemcitabine** may cause side effects, e.g. subfebrile body temperature, fatigue, myalgia, arthralgia, or paraesthesia. No reports of peripheral neuropathy induced by this drug in monotherapy have been found. A case study including such suggestions involved a carboplatin pre-treated patient [95]; therefore, it cannot be excluded that carboplatin was the source of complications. Gemcitabine is often combined with taxanes, platinum derivatives, and vinca alkaloids, i.e. drugs that often induce CIPN. Gemcitabine monotherapy has not been proved to be associated with the risk of peripheral neuropathy [96].

Side effects exerted on the central nervous system by **5-fluorouracil** (5-FU) were reported in 2-5% of patients [97]. Few CIPN cases were diagnosed during combined treatment with levamisole [98, 99] and eniluracil [100].

**Capecitabine** is metabolized to 5-FU; therefore, CIPN is not commonly diagnosed upon treatment with this therapeutic agent. Single cases of neurological complications have been described, including foot drop and mouth paraesthesia in pa-

tients undergoing pancreatic cancer treatment. More frequently, the drug is considered to cause palmar-plantar erythrodysesthesia, which is associated with local skin redness and swelling reaction appearing several days after initiation of therapy. The drug is excreted by the sweat glands of hands and feet and accumulated under the epidermis, thus causing inflammation. The syndrome is often accompanied by such symptoms as burning and stinging located in the same body parts. However, no permanent damage to the peripheral nervous system was found in this case [101, 102], and the reaction was reversible.

### Drugs from different therapeutic groups

Due to its toxicity, **suramin** is used rather infrequently at present. Damage to the peripheral nervous system involves the cell body, axon and myelin sheath [9, 103]; therefore, suramin-induced CIPN may assume the form of both peripheral and demyelinating neuropathy [104].

**Lenalidomide** is a thalidomide analogue inducing more severe side effects in the form of somnolence and neuropathy [105].

**Arsenic trioxide**, rarely used due to its toxicity, can cause dose- and axonal length-dependent neuropathies, which are partially reversible after discontinuation of the therapy [106]. **Tipifarnib** is mainly hepatotoxic, while neurotoxicity is not regarded as its major side effect [106, 107].

### Summary

The presented material illustrates the complexity of the problems associated with the pathophysiology of chemotherapy-induced peripheral neuropathy. The groups of drugs discussed here exhibit different mechanisms of anticancer action; hence damage to the peripheral nervous system proceeds in a variety of ways. Therefore, CIPN cannot be considered a homogeneous syndrome, although the symptoms are substantially similar. Investigations conducted so far have not provided conclusive results concerning prophylaxis and therapy schemes. Currently, the only effective method in the case of the syndrome is reduction of the dose or discontinuation of chemotherapy followed by symptomatic treatment.

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