PRACE POGLĄDOWE
ginekologia

Chemotherapy-induced peripheral neuropathy – epidemiology and pathogenesis

Obwodowa neuropatia indukowana chemioterapią – epidemiologia i patogeneza

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most important neurologic complications experienced by patients receiving chemotherapy. The neuropathy often interferes with daily activities and exercise leading to severe impairment of the patient's quality of life (QoL). The evolution of most CIPNs is characterized by a gradual onset of signs/symptoms, beginning in the lower limbs and advancing proximally into a bilateral stocking and glove distribution. Patients often complain of numbness, tingling and pain in the affected areas. The symptoms become aggravated with repeated cycles of chemotherapy. When the offending agent is withheld, the symptoms generally abate, but relief is not guaranteed. The consequences of delay or discontinuation of treatment may affect overall patient survival.

Key words: **cancer** / **pathogenesis** / **chemotherapy** / **epidemiology** / / **peripheral neuropathy** /

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Otrzymano: **04.11.2015**
Zaakceptowano do druku: **10.02.2016**

DOI: 10.17772/gp/61750

Streszczenie

Obwodowa neuropatia indukowana chemioterapią jest jednym z najważniejszych powikłań neurologicznych u pacjentek jej podanych, często zakłócając codzienne aktywności i upośledzając jakość życia a jej objawy pogarszają się przy powtarzanych cyklach chemioterapii. Omówiono stopnie nasilenia neuropatii (Tabela I), jej epidemiologię (szacuje się że doświadcza jej 30% do 55% pacjentów otrzymujących chemioterapię). Jej nasilenie i jakość zależy od czynników osobistego ryzyka (wcześniej istniejące neuropatie, choroby towarzyszące i operacje) i od stosowanego leku (jego typu, sposobu podawania, dawki itp).

Omówiono efekty podawania różnych czynników chemioterapii (docetakselu, winkrystyny, iksabepilonu, oksaliplatyny, cisplatyny, talodomidu, lenalidomidu, bortezomibu), różnice wrażliwości na neuropatię wynikające z polimorfizmu genowego, wieku pacjenta.

Słowa kluczowe: **patogeneza** / **epidemiologia** / **nowotwór** / **chemioterapia** / / **neuropatia** /

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most important neurologic complications experienced by patients receiving chemotherapy. The neuropathy often interferes with daily activities and exercise leading to severe impairment of the patient's quality of life (QoL). The evolution of most CIPNs is characterized by a gradual onset of signs/symptoms, beginning in the lower limbs and advancing proximally into a bilateral stocking and glove distribution. Patients often complain of numbness, tingling and pain in the affected areas. The symptoms become aggravated with repeated cycles of chemotherapy. When the offending agent is withheld, the symptoms generally abate, but relief is not guaranteed. The consequences of delay or discontinuation of treatment may affect overall patient survival.

CIPN Grading

Data from clinical examinations and subjective reporting from patients regarding the symptoms and severity of CIPN are compared against one or more grading scales to establish the degree of peripheral neurotoxicity. The severity of drug-related toxic side-effects in most of these scales is commonly assigned a grade between 0 (none) to 5 (death) (Table I).

Various toxicity scales in common use are the World Health Organization (WHO) scale, the National Cancer Institute - Common Toxicity Criteria (NCI-CTC) 3.0, the Ajani Score, and the Eastern Cooperative Oncology Group (ECOG) scale. Other, more neurologically specific scales used during clinical trials for new agents include the Neuropathy Symptom Score, the Neuropathy Impairment Score, and the Total Neuropathy Score - TNS [9],[12],[15]. The TNS has shown to be easy in use, compared to the other scales while providing more specific information about characteristics of the neuropathy [12] than general toxicity scales did. There are two basic variants of the TNS: the reduced one (TNSr), which uses electrophysiological data and the other, purely clinical TNSc [12]. Non-uniform criteria in each of the scales give rise to comparative ambiguities between them.

Epidemiology

The reported incidence of CIPN is variable, but estimates are between 30 to 55% of the patients receiving chemotherapy [12]. The severity and quality of CIPN can be influenced by both agent- and patient-specific risk factors. Agent-specific factors include: type of agent, dosage, infusion rate and schedule, route of administration, total cumulative dose, combination therapy, and pharmacokinetic profile [15], [16], Patient-specific factors include: pre-existing neuropathies, comorbidity and surgery [15] [28],[30],.

More than 90% of breast cancer patients with previous exposure to chemotherapy with paclitaxel indicated a TNS of grade 2 (symptomatic but not severe one) [18] with only few patients manifesting the grade 3 [7]. Among ovarian cancer patients treated with a carboplatin/paclitaxel regimen more than half (54%) experienced CIPN. The neurotoxicity is dose related and progresses with higher doses of chemotherapy. Incidence of paclitaxel-related CIPN occurs most often when the dose per cycle exceeds 250 mg/m^2. It is not clear whether duration of infusions, i.e. over 3 or 24 hours makes any difference in terms of CIPN prevalence and severity. There is no consensus either regarding cumulative doses triggering symptoms of neurotoxicity.

Docetaxel has a similar toxicity profile to paclitaxel but side effects are generally considered milder, possibly as a result of lower administered doses. Patients commonly receive docetaxel in one hour intravenous infusions of 100mg/m^2 doses, three times per week. Cumulative doses of about 400 mg/m^2 can trigger severe symptoms, with some patients manifesting Lhermitte's sign and a proximal motor weakness.

Vincristine is the only chemotherapeutic agent for which neurotoxicity is uniformly experienced in all recipients [22]. It is commonly used in combination with other anti-tumour drugs and current doses vary between 2-4 mg every 3-4 weeks. Cumulative doses of 5-6 mg trigger the earliest signs of neurotoxicity. The most intense symptoms were reported at the threshold of 12 mg. Other vinca derivatives, such as vindesine and vinblastine are less neurotoxic. Neuropathy findings, based on dosages and treatment length for vincristine are shown in Table II.

One of the epithelones, **ixabepilone**, also triggers neuropathy, which was reported in 63.6% of patients, affected mainly by gynecological tumors [26].

Neurologic toxicity is frequent in **oxaliplatine** therapy, in which it can appear in up to 97% of individuals. There are two distinct forms of oxaliplatine-related neurotoxicity, which follow one after the other. The first one emerges rapidly and is predominantly sensory and rather transient that and it may reappear after subsequent infusions. It is followed by a more

Table I. CIPN grading scale.

Grade	0	1	2	3	4	5
Motor neuropathy	Normal	Asymptomatic, weakness on examination only.	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated (e.g. cane or walker)	Life-threatening consequences; urgent intervention indicated. Disabling	Death
Sensory neuropathy	Normal	Asymptomatic loss of deep tendon reflexes or parenthesis	Moderate sensory symptoms; or parenthesis limiting instrumental ADL	Severe symptoms; sensory alterations or parenthesis limiting self-care ADL	Life-threatening consequences; urgent intervention indicated. Disability	Death
Neuralgia		Mild Pain	Moderate pain limiting instrumental ADL	Severe pain limiting self-care ADL		

A grade greater than "2" is associated with a decline in the quality of life of a cancer patient.

Table II. Vincristine neuropathy depending on dosage and cycles.

Patients	Treatment	Cycles	Intensity (mg/m²/week)	Incidence
27	1.6 mg/m² every 21 days	6	0.47	Grade 1-2: 22%
11	1.4 mg/m², twice every 21 days	3	0.94	Grade 1-2: 63.6%
				Grade 3-4: 36.4%
11	1.5 mg/m² every 7 days	8	1.5	Grade 1: 9%
				Grade 2: 73%
				Grade 3-4: 0%
31	2 mg/m² every 7 days	4	2	Grade 2-3: 45%

progressive and persistent neuropathy. Neuropathy findings based on dosages and treatment length for oxaliplatin and cisplatin are shown in Tables III and IV.

Thalidomide is an anti-angiogenic drug used in treatment of diseases associated with angiogenesis, like multiple myeloma. It is frequently associated (up to 70% of cases) with a peripheral neuropathy (PN), the mechanism of which remains unknown [25]. The most common presentation of thalidomide-induced PN is distal parenthesis and/or dysesthesias with or without sensory loss [20].

The thalidomide analogue, **lenalidomide** is an immunomodulatory drug, which is used in the treatment of myelodysplastic syndrome with 5q deletion and in multiple myeloma (MM), and it seems to be more potent and to manifest a milder toxicity profile, including reduced risk of inducing CIPN [20]. **Bortezomib**, a new chemotherapeutic agent used mainly in the treatment of multiple myeloma, was also reported to cause peripheral neuropathy [33], [4]. Its incidence was estimated at 52%, ranging from TNS of grade 1 to 4.

Preexisting peripheral nerve disease

Individuals with pre-existing neuropathy do not necessarily experience more often adverse effects of chemotherapy treatment, but case studies indicate a predisposition toward a more severe neurotoxicity [17], [28]. In addition to inherited diseases, such as CMT, influencing severity of CIPN, other genetic traits also show susceptibility to peripheral nerve toxicity.

Gene polymorphisms

Gastrointestinal cancer patients with common polymorphisms in glutathione-S-transferase (GST) variants: GSTP1, GSTT1, and GSTM1 genes were examined to predict the risk of cumulative oxaliplatin-associated neuropathy. The investigation revealed that a polymorphism of the GSTP1 gene had an influence on the risk of severe neuropathy in these patients. Homozygous GSTP1 *A/*A haplotype class of patients exhibited more grade 3 neuropathy. Thus, the GSTP1 genotype in gastrointestinal cancer patients may become a useful tool in risk assessment for cumulative oxaliplatin-induced neuropathy and safer chemotherapy regimens.

Age-related susceptibility

Advanced age is often assumed to be associated with an increased susceptibility to neurotoxic agents and a higher likelihood to adverse events, including CIPN. However, there is insufficient evidence to support or refute this assertion. Finally, aggravation of peripheral neuropathy symptoms was noted post-operatively in a small group of metastatic colorectal cancer

DOI: 10.17772/gp/61750

Table III. Oxaliplatin neuropathy depending on dosage and cycles.

Number of patients	Treatment	Cycles	Intensity (mg/m²/week)	Incidence	Reference
1108	85mg/m² every 14 days	12	42.5	Grade 1: 46%	[2]
				Grade 2: 33.6%	
				Grade 3: 12.4%	
1321	85mg/m² every 14 days	12	42.5	Grade 2: 29%	[1]
				Grade 3: 14%	
452	130mg/m² every 21 days	8(max)	43.33	Grade 1-2: 75.2%	[21]
				Grade 3-4: 6.4%	
69	130mg/m² every 21 days	8	43.33	Grade 2: 42%	[21]
				Grade 3: 16%	

Table IV: Cisplatin neuropathy depending on dosage and cycles.

Number of patients	Treatment	Cycles	Intensity (mg/m²/week)	Incidence	Reference
261	50mg/m² every 21 days	6	16.7	Grade 1: 24.9%	[31]
				Grade 2: 3.1%	
				Grade 3: 1.9%	
				Grade 4: 0%	
129	50mg/m² every 21 days	7	16.7	Grade 1-2: 3.1%	[24]
				Grade 3-4: 0.8%	
119	80mg/m² every 21 days	5	26.7	Grade 1: 14%	
				Grade 2: 8%	[24]
				Grade 3-4: 1%	
21	100mg/m² every 21 days	6	33.3	Grade 1: 33.3%	[34]
				Grade 2: 33.3%	
				Grade 3: 19%	
				Grade 4: 0%	

patients who had been heavily pretreated with oxaliplatin [27]. Seven of 12 patients who developed immediate post-surgical symptoms of CIPN had undetectable oxaliplatin serum levels before surgery but high post-surgical serum concentrations. The explanation for exacerbated CIPN most likely involved the accumulation of di-chloro-DACH platinum (a biotrasformation product of DACH platinum) in erythrocytes, which might have been released into the plasma via perioperative hemolysis. This suggests that surgery may be a risk factor of CIPN for patients pretreated with chemotherapy.

Pathogenesis

Although the pathophysiological mechanism of CIPN is not completely understood, it has been shown that cytotoxic activity of chemotherapy agents affects mainly the axons and Schwann cells. A temporary, functional impairment or destruction of cells in dorsal root ganglia (DRG) may also occur. There are various factors which predispose to these cytotoxic insults: susceptibility to damage is associated with diameter, length, and myelination of nerve fibres. Somatosensory axons responsible for pain and temperature perception, and smaller diameter autonomic nerves having poor or no myelination, are more vulnerable compared to motor axons. Most motor neurons have larger diameters and are highly myelinated. Motor neuron involvement occurs only if sensory symptoms are present and often accompanies more severe or persistent cases [29]. The longest peripheral nerves are the first to be affected. Penetrance of the dorsal root ganglia (DRG) is facilitated by the fact that the blood-nerve barrier is more permeable than blood–brain barrier in the CNS. Another factor which makes them more sensitive is the absence of lymphatic vessels, which renders removal of toxins from the endoneural space inefficient [29].

When neurotoxins diffuse along the nerve fibres, damage occurs in the neuron cell bodies in the DRG, the axons, myelin sheath and supporting glial structures [29]. The mechanism of this damage depends on the agent type. In chemotherapy, the

Table V. Chemotherapeutics inducing peripheral neuropathy.

Agent	Dosage	Triggering dose	Cumulative triggering dose	Severity	Comments	Reference
Ixabepilone	40 mg/m^2 During 1h repeated every 3 weeks			Grade 1 – 38.6% Grade 2-3 – 25% Grade 2-3 – 30%		[26]
Oxaliplatine	85 mg/m^2 every 2 weeks	85 mg per m^2	≥540 mg/m^2		Carboplatin is regarded to be the safest derivative in this group	[14]
Thalidomide	100mg once daily			Peripheral neuropathy is observed in up to 70% of patients		[20] [25]
Lenalidomide	30mg once daily or 15mg twice daily on days 1-21 of a 28 day cycle			Grade 3 – 3%	Less toxic than thalidomide	[57]
Bortezomib	1.0 or 1.3 mg/m^2 twice a week, for 2 weeks, in cycles repeated every 3 weeks	Usually till fifth cycle	30 mg/m^2			[4]

Table VI. Risk factors for chemotherapy-induced peripheral neuropathy.

Risk factors for CIPN	
Agent-dependent	**Patient-dependent**
• type of agent, • dosage, • infusion rate and schedule, • Total cumulative dose.	• Comorbididies (diabetes mellitus, Charcot-Marie-Tooth disease) • GSTP1 *A/*A haplotype in gastrointestinal cancer • Chemotherapy prior to surgery

common drug classes responsible for CIPN depending on their mechanism of action may be divided into the following groups:

- DNA alkylating agents (platinum compounds),
- microtubule targeting agents,
- mitotic spindle inhibitors (vinca alkaloids),
- microtubule hyperstabilizing agents (taxanes, epithelones),
- other agents, such as proteasome inhibitors (bortezomib).

DNA alkylating agents

At the cellular level, chemotherapy agents interfere with metabolic functions of neurons, leading to irreparable mitochondrial injury and apoptosis. This resembles the effects of chemotherapy agents on cancer cells. Axonal metabolism becomes impaired and Wallerian degeneration of the axon begins at the distal ends and eventually it advances proximally. This explanation is supported by a study involving platinum-induced peripheral neuropathy in rats treated with cisplatin. After 9 weeks, evidence of cisplatin in the DRG, accompanied by morphologic changes, was detected using polyclonal antibodies. Platinum agents bind DNA in the DRG and trigger apoptosis of neurons. The electrophysiological studies of oxaliplatine neurotoxicity revealed two distinct responses. The first chemotherapy cycle triggered neuronal hypersensitivity within hours of oxaliplatin infusion.

Its explanation involves the impairment of potassium-gated ion channels since similar symptoms were observed in neuromyotonia. The other response occurs after a few cycles of oxaliplatin and manifests as a sensory axonal neuropathy. This is likely related to accumulation of platinum compounds in cell bodies of DRG.

Microtubule targeting agents

Taxanes, vinca alkaloids, podophyllin analogs, and epithelones are anticancer drugs commonly associated with CIPN. Sensory, motor, and autonomic fibres are all affected by these microtubule targeting agents (MTAs). At the cellular level, microtubules are important functional (transport of proteins, vesicles and other organelle) and structural (cytoskeleton) components of neurons. MTAs interfere with the polymerization and depolymerization of microtubules in cells, resulting in a crippled axonal transport system. Thus, MTAs disrupt metabolic function in neurons, triggering apoptotic mechanisms. The actions of MTAs can be classified as either microtubule hyperstabilizing or microtubule destabilizing [19]. The taxane derivatives (paclitaxel and docetaxel) promote hyperpolymerization of large, disordered arrays of microtubules in DRG neurons, axons, and Schwann cells. Microtubule hyperstabilizing agents include also epithelones and their analogs.

DOI: 10.17772/gp/61750

Table VII Clinical pattern of drugs most frequently associated with CIPN.

Drug	Motor functions	Sensory functions	Reflexes	Autonomic
Cisplatin	Not affected	35% of patients. Distal, symmetric, upper and lower limb loss of all modalities. Painful neuropathy	Corresponding to sensory loss	Rare
Carboplatin	Not affected	15% of patients, less prominent than with cisplatin. Pain is less common than with cisplatin	As above	As above
Oxaliplatin (acute)	Possible cramps (in throat muscles)	80% of patients. Cold-induced dysesthesia (mouth, throat, upper limbs)	As above	As above
Oxaliplatin (chronic)			As above	As above
Vincristine>vinblastine, vindesine, vinorelbine	5-10% patients, distal symmetric weakness - foot drop	35% of patients, loss of all modalities in lower limbs, upper limb involvement uncommon	Early reduction or abolition	Constipation, orthostatic hypotension
Docetaxel, paclitaxel	Rare, mild weakness in the feet	Mild distal loss in the feet	Decreased ankle reflexes	Uncommon
Bortezomib	5-10% patients, mild distal weakness	35% of patients moderate distal symmetric loss of all modalities in the lower limbs	Corresponding to sensory loss	Uncommon
Thalidomide	Rare	30% of patients, mild to moderate distal symmetric loss of all modalities in the lower limbs	Corresponding to sensory loss	Uncommon

Taxanes promote polymerization of tubules by binding to beta-tubulin and locking the structures in place [3]. Studies have demonstrated *in vitro* and *in vivo* their direct effects on Schwann cells and a disrupted axonal flow in affected neurons. The experimental data showed that paclitaxel injected to DRG cells triggered accumulation of microtubules. At the same time an interruption of anterograde transport was observable. An intravenous paclitaxel administration also caused microtubule accumulation [10] and clinically observable neuropathy [35]. The pathology was reversible and there was no degeneration of neurons [10]. The nerve biopsies from patients presenting paclitaxel-induced neuropathy, however, reveal different alterations, namely axonal loss and atrophy as well as demyelination.

In contrast to the taxanes, vinca alkaloids are microtubule destabilizers. Vincristine was shown in rats to shorten microtubules, leading to an inability for the microtubule elements to maintain normal longitudinal orientation. This triggered a collapse in the cytoskeleton array and accumulation of vesicles proximal to the targeted axonal segment, leading to disruption of fast axoplasmic transport. The neurofilaments were accumulated in the cells of DRG.

The process of neural degeneration also involves proteins called calpains. These calcium-dependent proteolytic enzymes are activated by a transient and localized influx of calcium ions into the cell. The signal transduction pathway is then advanced by catalyzing the controlled proteolytic processing of target proteins. Their activation appears to increase the rate of neural degeneration. In one study, mice underwent paclitaxel therapy and received an inhibitor of calpain activation (AK295). The number of degenerated axons was significantly lower in the group receiving AK295 compared to the control group and clinical testing revealed a reduced level of deterioration. Similar results were obtained in vincristine therapy. This suggests that interference with cellular transport, triggered by MTAs, is not the only mechanism engaged in the pathology of CIPN.

Thalidomide is an anti-angiogenic drug, which also acts through immunomodulation including cytokine modulation. The exact mechanism of peripheral neuropathy remains still unknown.

Bortezomib is a reversible inhibitor of the 26S proteasome, a macromolecule involved in the ubiquitine-targeted degradation of proteins. One of the proteins degraded by the 26S proteasome is the inhibitor of nuclear factor NFkB. The inhibition of the 26S proteosome by bortezomib increases the level of the NfkB inhibitor, and therefore, has a suppressive influence on NfkB. When various signal transduction pathways are inhibited, reduced cellular transcription of many proteins occur, including those responsible for cell cycle regulation and apoptosis: neoplastic tissue angiogenesis is inhibited and apoptosis increases [33],. A few mechanisms of bortezomib neuropathy were suggested. Intracellular calcium ion homeostasis is significantly disrupted within cells exposed to bortezomib. Such a condition may lead to mitochondrial dysfunction and may activate the apoptotic pathway [4]. Interference of transcription may also lead to down-regulation of nerve growth factor level. Pathological findings in animal models have revealed damage to Schwann cells in the sciatic nerve and satellite cells in the DRG [11].

In order to summarize, in Table IV we present the most common clinical pattern observed in patients treated with anticancer neurotoxic drugs

Closing remarks

A good understanding of the processes underlying the chemotherapy-induced polyneuropathy depends, among other, on the employed diagnostic procedures. It conditions an appropriate treatment and allows defining the most plausible management of the disorder in a given patient. These problems will be addressed in the forthcoming article.

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3. Maciej Kaźmierczak – współautor tekstu pracy, korekta i aktualizacja literatury.
4. Ewa Nowak-Markwitz – współautor tekstu pracy, korekta i aktualizacja literatury.

Źródło finansowania:

Praca nie była finansowana przez żadną instytucję naukowo-badawczą, stowarzyszenie ani inny podmiot, autorzy nie otrzymali żadnego grantu.

Konflikt interesów:

Autorzy nie zgłaszają konfliktu interesów oraz nie otrzymali żadnego wynagrodzenia związanego z powstawaniem pracy.

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