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Chapter

Chemotherapy-Induced Peripheral Neuropathy: Mechanisms and Clinical Assessment

Jordi Casanova-Mollà

Abstract

Antineoplastic drugs may be neurotoxic and the clinical features frequently include distal sensory loss and neuropathic pain. This is related to a direct damage in sensory neurons and non-selective degeneration of sensory nerve fibers. Due to different mechanisms, there are agents that affects also motor or autonomic nerves. In the case of immune checkpoint inhibitors, an inflammatory response attacks the muscle, motor neurons or neuromuscular transmission. We present an easy-to-read article to understand first symptoms of chemotherapy-induced neuropathy (CIN) with describing each agent and the course of neuropathy as well as the clinical assessment with neurophysiological techniques. In addition, skin biopsy allows us to examine histological changes such as reinnervation. Neuroprotection with antioxidant therapy is possible but more effort in this field is needed.

Keywords: chemotherapy-induced neuropathy, oxaliplatin-induced neuropathy, neurotoxicity, polyneuropathy, toxic neuropathy

1. Introduction

Currently the chemotherapeutic drugs are part of cancer treatment. Among their side effects, neurotoxicity at peripheral nervous system is a well recognize dose-limiting side effect. It is relevant because it causes persistent pain and sensory loss in cancer survivors. The prevalence of chemotherapy-induced peripheral neuropathy (CIPN) has been reported around 30% of patients at 6 months after treatment. It reaches up to 40% when patients are also examined with nerve conduction studies [1]. It is important to note that neurotoxicity could be subclinical, it means that it may start before patient starts to be symptomatic.

The clinical picture at presentation of CIPN is a length-dependent sensory polyneuropathy despite other combination of sensory, motor and autonomic nerve dysfunction are possible. It is important to recognize different types of sensory nerve fibers which are specific to different sensory modalities (touch, vibration, temperature and pain). All of these neurons have their cell bodies in the dorsal root ganglion (DRG). The thin-myelinated Aδ fibers and unmyelinated C fibers are known as small nerve fibers carrying thermal and painful stimulus to the brain. We need selective neurophysiological and histological techniques to evaluate them as well as to examine the function of the autonomic nervous system [2].

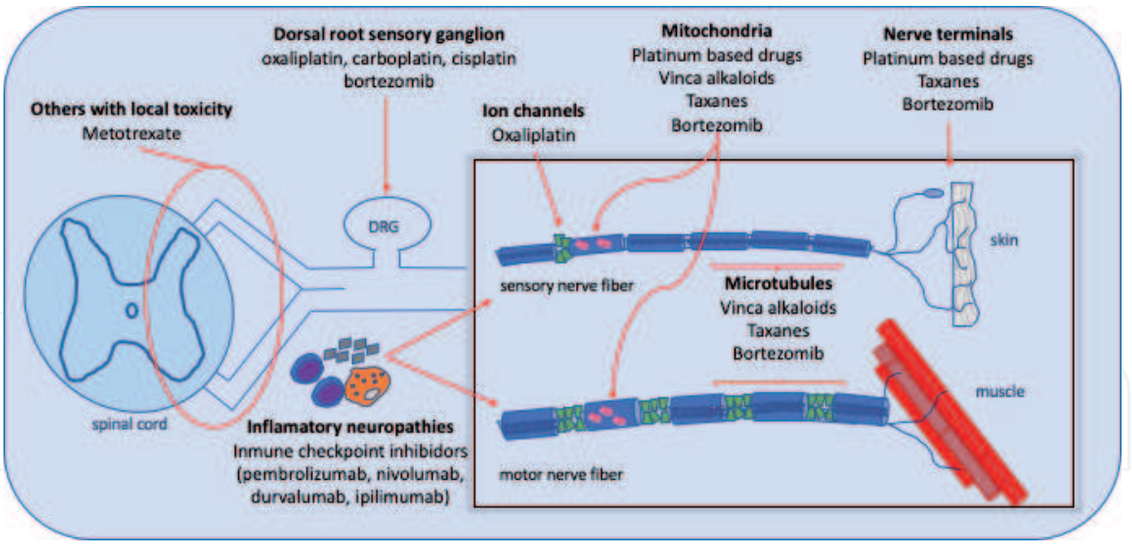

Figure 1.
Different targets to produce neurotoxicity by chemotherapy.

Drug	Main mechanism of action	Mechanism of neurotoxicity	Tumor
Platinum salts (oxaliplatin, carboplatin, cisplatin)	Alkylation of DNA	Ion channels hyperexcitability, neuronal DNA damage, loss of axonal transport, mitochondrial dysfunction, neuroinflammation	digestive tract tumors, pulmonary, ovarian, testicular, uterine, SCLC
Taxanes (paclitaxel, docetaxel)	Microtubule stabilizer	Loss of axonal transport, neuroinflammation, damage of mitochondrial DNA, ion channel hyperexcitability	breast, gynecologic, gastric, NSCLC prostate, sarcomas
Vincristine, Vinblastine	Microtubule stabilizer	Loss of axonal transport, neuroinflammation	lymphoma, testicular, NSCLC
Bortezomib	Proteasome inhibitor; microtubule stabilizer	Mitochondrial damage, accumulation of aggregates, DNA damage, increase sphingolipid metabolism	multiple myeloma, lymphomas
Thalidomide, Lenalidomide,	Immunomodulator and antiangiogenic effect	Oxidative stress, downregulation of TNF-α, inhibits NF-κB	multiple myeloma
Brentuximab	Immunomodulator (anti-CD30)	Loss of axonal transport	lymphomas
Check-point inhibitors (ipilimumab, pembrolizumab, avelumab)	Immunomodulator effect against cytotoxic T-lymphocyte	Immune-related neuropathies; vasculitic neuropathy (pembrolizumab)	melanoma
Methotrexate or Cytarabine intrathecal	Dihydrofolate reductase inhibitor	Spinal cord and proximal roots demyelination	leukemia and lymphomas

SCLC = small-cell lung cancer; NSCLC: non-small cell lung cancer.

Table 1.
Classification of commonly used chemotherapy drugs related to elevated risk of CIPN.

The most neurotoxic families of chemotherapeutic drugs are the platinum derivates (e.g. oxaliplatin, carboplatin or cisplatin), taxanes (e.g. paclitaxel and docetaxel), vinca alkaloids (e.g. vincristine), proteasome inhibitors (e.g. bortezomib) and immunomodulators (e.g. thalidomide and checkpoint inhibitors). Others, as methotrexate or arsenic salts are less frequently used. See **Figure 1** a general schema with different targets on the peripheral nervous system and in **Table 1** a list of them with their mechanism of neurotoxicity.

2. Acute neurotoxicity

There are drugs that can produce acute neurotoxicity, a side effect commonly seen with oxaliplatin. It is characterized by transient paresthesia, dysesthesia and muscle cramps induced by cold exposure, a phenomenon often called cold allodynia that typically appears during or immediately after infusion of the treatment. It usually resolves within a few hours or days before the next oxaliplatin cycle [3]. Symptoms reported by patients include tingling paresthesia in the hands (100%), feet (42%) and orofacial area (50%) and also, pharyngeal or laryngeal regions, all of them triggered by cold (especially when drinking). More infrequently, patients report fasciculations (29%), jaw spasms (26%), cramps (20%), difficulty of swallowing (18%) and neuromyotonia-like syndrome. All these phenomena reveal an increase in sensory and motor nerve excitability related to the impairment of voltage-gated sodium channels induced by oxaliplatin [4]. A functional study demonstrated that oxaliplatin induces reversible slowing of sodium channel inactivation [5]. We know that it does not require discontinuation of treatment or dose reduction, but prolonging the time of infusion from 2 h to 4 or 6 h is recommended [6]. Some authors have found a relationship to later develop of chronic neuropathy [7, 8]. In particular when cold allodynia persists for days or weeks after infusion. Even some patients, continued to report residual symptoms in subsequent doses of oxaliplatin [9]. Another symptom that patients frequently ask is the Lhermitte's sign, a sudden lightening sensation radiate out into both arms or feet when neck flexion is forced. The mechanism to produce it at cervical spinal cord is unknown but usually self-limited despite in some exceptional cases it could appear lately and be persistent during months [10, 11].

It has been described in addition acute sensitization of nociceptors with paclitaxel, the paclitaxel-associate acute pain syndrome. It consists of aching or other pain sensations mainly at lower legs peaked on day 4 after paclitaxel initiation. This is related to fast infusion of treatment (3 hours) but also, indicates more risk to sensory neuropathy after 12 weeks of therapy [12].

3. Targets of neurotoxicity at peripheral nerves

Even when all body is exposed to chemotherapy, there are tissues more vulnerable to chemotherapy than others. This is the case of sensory neurons located at dorsal root ganglion (DRG) which are outside the protection of the blood–brain barrier. They are the principal targets of platinum derivates such us oxaliplatin, cisplatin or other platinum agents. Thus, neurons are damaged directly at DRG producing a progressive sensory neuronopathy. However, neurotoxicity also causes multiple lesions within the axons both for platinum agents and for other drugs as taxanes generating distal axonopathy. This will have different consequences for patients.

On one hand, the myelinated sensory nerve fibers lose their function. This is noted by many patients in a "glove and stocking" pattern of sensory loss involving

hands and feet. They frequently refer reduced precision to make fine movements with tip of the fingers which is noted by having less ability to cross buttons when dressing or when typing the computer. Also, gait disturbances affect their daily activities because of instability when walking in irregular ground or for descending stairs. On the other hand, thin myelinated (Aδ fibers) and unmyelinated (C fibers) carrying the information of temperature and pain are also damaged. A combination of negative and positive symptoms (see **Figure 2**) contributes to sensory disturbances. The unpleasant dysesthesias and neuropathic pain are consequence of the gain of function in damaged sensory nerve fibers that increases their excitability by producing spontaneous burning sensation or electric shock-like pain.

This clinical picture is common for all chemotherapy agents despite the mechanisms may differ among them. Also, it may determine the severity of axonal loss and its recovery since regeneration is expected to occur if the axon is affected distally whereas poor should be assumed in a neuronopathy. In general, we use the term sensory polyneuropathy for CINP when symptoms have a characteristic distance-dependent pattern even when we know that it is combined with sensory neuronopathy which has been demonstrated for oxaliplatin and cisplatin [13, 14].

There are other drugs such as vincristine, bortezomib or arsenic salts with ability to produce a more generalized axonal damage in all nerves. In this case, sensory deficits are accompanied by frequent muscular cramps, predominantly at night in both legs as well as distal weakness in upper and lower extremities because of motor neuropathy. Moreover, the failure in autonomic nerves leads to chronic constipation, reduced distal sweating and dizziness when standing (orthostatic hypotension) due to autonomic neuropathy or dysautonomia.

More recently, the introduction of the checkpoint inhibitors as a treatment for advance melanoma have opened the possibility of different immune-mediated neuromuscular manifestations reported as complication of the treatment in 75% of

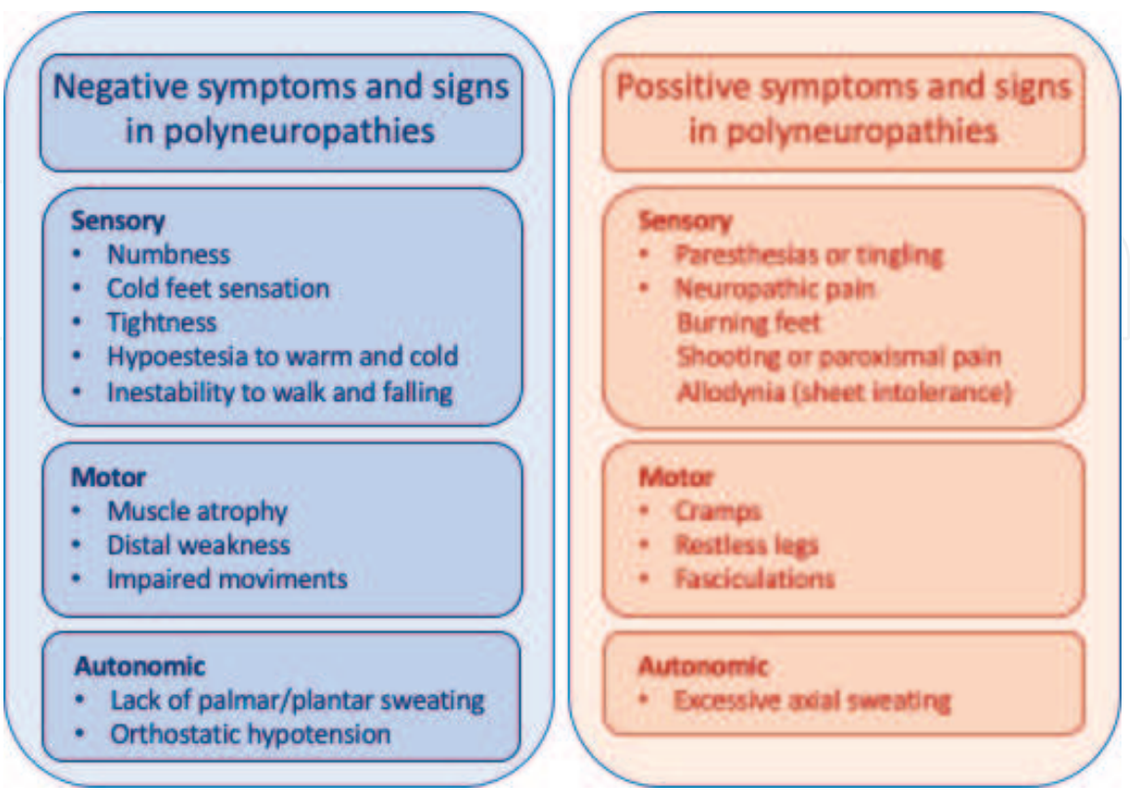

Figure 2.
Comparison of positive and negative symptoms in CIPN.

patients [15]. In this case acute demyelinating polyneuropathy (Guillain-Barré syndrome), demyelinating sensorimotor neuropathy, myositis or myasthenic syndrome have to be considered.

The combination of peripheral and central neurotoxicity at spinal cord should be considered in intrathecal infusion of chemotherapy. This is necessary for patients with acute leukemia treated with methotrexate. It has been described also after vincristine treatment. In this case, proximal motor roots can be unexpectedly block with a variable extension of myelitis at the level of lumbar infusion producing a complete paresis in lower limbs (paraparesis) with a lower abdomen level of sensory loss together with urinary dysfunction. This is a devastating situation that has been reported in few cases with poor prognosis for recovery [16, 17].

4. Risks and other conditionings for CIPN

It is difficult to establish in humans exactly the timing of changes on peripheral nerves after a pharmacological insult. Even though we know the day chemotherapy starts, there are different risk factors than makes neuropathy more probable in one patient than another. In **Table 2** are listed the most known of them. In particular, one of such factors is the cumulative dose, especially for platinum agents. It was demonstrated that high-dose cisplatin was intrinsically more neurotoxic [23]. There is a range between 300 and 400 mg/m^2 from which sensory symptoms starts to be persistent and from 540 to 850 mg/m^2 from which the CIPN is generally stablished with high risk to be a long-term condition. However, we know now that there is no specific dose to be secure and probable neurotoxicity starts from first dose with a cumulative effect within sensory neurons.

Factors associated to higher risk of CIPN	Evidence	Type of study	Reference
Age	Low	Retrospective	[18]
Type of cancer	No evidence	Observational	[10]
Smoker	No evidence	Observational	[10]
Alcoholic	No evidence	Observational	[10]
Pre-chemotherapy neuropathy			
Diabetes	High if diabetic neuropathy	Retrospective	[6, 18]
Hereditary neuropathy	High	Retrospective	vincristine [19]
Cancer-induced neuropathy	High	Observational	[10, 20–22]
Dose of chemotherapy	Very High	Observational Experimental	[13, 14, 23]
Acute cold allodynia	High	Retrospective Observational	[7, 8, 9]
Repeated chemotherapy	Moderate	Observational	oxaliplatin [24]
Association with other chemotherapy	Very High		cisplatin+vincristine [18] cisplatin+paclitaxel [25] bortezomib-thalidomide [26]

Table 2.
General risk factors for CIPN.

One phenomenon that usually appears with platinum agents (cisplatin and oxaliplatin) is the coasting effect. It refers to the further progression of neurotoxicity during 3 to 6 months after stopping the treatment that results from its capacity to accumulate in DRG for a long time. It was described first for cisplatin [18, 27, 28] and later for oxaliplatin [9, 29, 30]. This surprises the patient who frequently ask worried because of deterioration of their sensory deficits after treatment was stopped.

5. Clinical assessment for early detection of CIPN

A good complement for clinical examination is the use of validated scales. It allows systematic data acquisition which is comparable in the follow-up of patients and also, their inclusion in research studies. There are different types of scales, ones are self-administered, others are based on clinical examination or they include a combination of clinical and results of complementary tests. We will comment two of the most used scales for CIPN and one self-administered scale.

The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) includes a scale based on the degree of impact of peripheral sensory neuropathy which is the most widely used scale used by oncologists [31]. It grades from 1 to 5 patient's functionality disturbance due to sensory symptoms of neuropathy. There are different versions which are updated by the Division of Cancer Treatments and Diagnosis. The version 4.03 published in 2009 is currently the most referenced in last publications. The 5 grades are: 1) asymptomatic (weakness or loss of tendon reflex on examination) or paresthesia not interfering with function; 2) symptomatic or sensory alterations interfering with function but not with daily activities; 3) weakness or sensory alterations interfering with daily activities; 4) life threatening disabling; 5) death.

	0	1	2	3	5
Sensory symptoms	None	Symptoms limited to fingers or toes	Symptoms extends to ankle or wrist	Symptoms extends to knee or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/ assistance	Paralysis
Autonomic symptoms	0	1	2	3	4 or 5
Pin sensibility	Normal	Reduced in fingers or toes	Reduced up to wrist/ ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Vibration sensibility	Normal	Reduced fingers or toes	Reduced up to writs/ ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Strenght	Normal	Mild weakness	Moderate weakness	Severe	Paralysis
Tendon reflex	Normal	Ankle reflex reduced	Ankle reflex abset	Only	All reflexes absent

Note: Ranged from 0 to 28. CINP is significant if score > 5 points [32].

Table 3.
TNS clinical (TNSc) scale useful for the follow-up of patients.

The second most used scale for CIPN is the total neuropathy score (TNS). Its complete version was originally developed and validated for diabetic neuropathy. It combines clinical information obtained from grading symptoms and signs with neurophysiological parameters as nerve conduction studies and quantitative evaluation of sensory modalities. The clinical version (TNSc) includes the first 7 items (range 0 to 28) which are based only on clinical examination. It is showed in **Table 3**. A good correlation was reported between both, TNSc vs. NCI-CTCAE [32] even when TNSc is more sensitive in detecting mild sensory damage [33].

However, assessment of CIPN needs to involve subjective and objective information as well as the impact of the symptoms on functional activity. With this purpose, the European Organization for Research and Treatment of Cancer (EORTC) developed the self-administered scale QLQ-CIPN20. It includes 20 items in the form of auto-administered questions consisting of 3 scales (sensory, motor and autonomic). Each item range 1 (not at all) to 4 (very much) and a higher score is equivalent to worse or more symptoms during the past week. It should provide valuable information on CIPN-related symptoms and functional limitations of patients at risk [34].

6. Neurophysiological assessment for early detection of CIPN

There are different non-invasive techniques that provide information regarding the type of nerves (motor, sensory or autonomic) involved in CIPN. This is important to confirm the diagnosis but also to identify early markers of axonal damage and additionally, it may help to establish the prognosis for recovery.

6.1 Nerve conduction studies (NCS)

Peripheral nerves usually can be easily stimulated by electrical stimulus and brought to action potential. It can be applied to sensory or motor nerves. We measure the amplitude which reflects the amount of excitable axons, and the latency of the response to calculate the velocity conduction. It is essential to note that both, latency and velocity conduction reflect only the fastest conducting fibers. On the other hand, low amplitude of the sensory nerve potential indicates severe axonal loss [35]. In **Figure 3** there are examples of sensory nerve action potentials from a patient with sensory polyneuropathy after treatment with oxaliplatin.

The reduced amplitudes at sensory nerves with no significative changes in velocity conduction and motor responses are the common finding after treatment with platinum agents and taxanes. It affects distally sensory nerves at both sides in feet and hands. The sural nerve measured at ankle shows higher changes that other nerves such us radial or cubital nerves [36]. However, it is possible that the amplitude for sural nerve will fall within normal reference values, especially after treatment with oxaliplatin and taxanes in which sensory damage is limited to fingers or sole of the foot. The recording of the dorsal sural nerve is also recommendable to demonstrate low amplitudes in sensory distal polyneuropathy [37] (see **Figure 3a**). Nevertheless, not having normative values for such a distal nerve and the absence of response expected in the majority of the patients with CIPN makes results in amplitude necessary to be interpreted in relation to those obtained proximally at sural nerve in the same patient. If sensory symptoms are limited to hands, median entrapment neuropathy should be also rule out. Long-term follow up of patients after oxaliplatin showed persistent low amplitudes at sensory nerves 3 year after treatment [38].

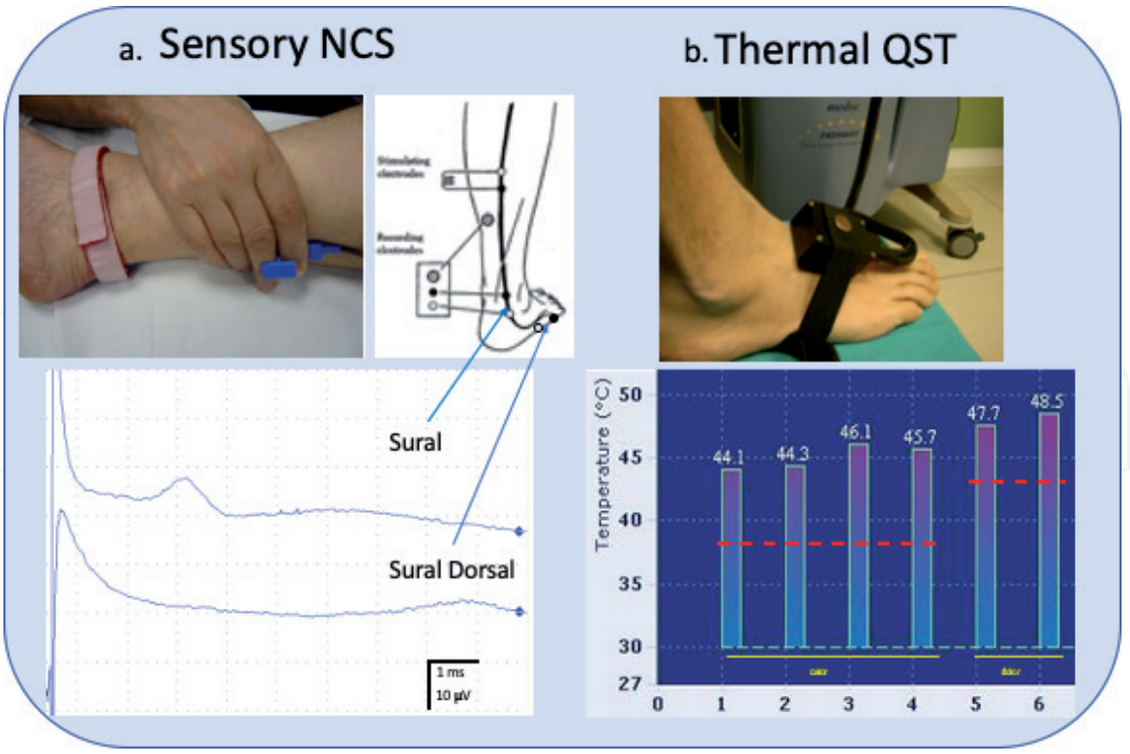

Figure 3.
Different techniques for diagnose CIPN. This figure shows two of the most common techniques (nerve conduction studies and thermotest) at evaluating the sensory function in suspected CIPN. a) the conventional sural nerve response, which is within normal limits (above) is compared with the more distal recording of the sural dorsal (below), which is clearly diminished; b) the thermode is applied at dorsum of the foot to test warm detection threshold (1–4 stimuli) and hot pain threshold (5–6 stimuli). Horizontal red line indicates normal values. The recording shows high thresholds to both, warm and pain. Note that detection of warm is near pain sensation because of the loss of function in C-fibers.

Other chemotherapy agents such us bortezomib or thalidomide produce a severe sensorimotor polyneuropathy with low amplitudes to all tested nerves. Despite axonopathy is the most frequent finding, in some cases a demyelinating pattern with reduced conduction velocities and prolonged proximal motor response (F-wave) may be possible (i.e., for example, 3 of 26 patients reported by Chaundhry [26]). The presence of signs of denervation in distal muscles at lower limbs is expected on EMG as well as atrophy of muscles together with weakness and instability to walk due to sensory deficits at feet.

6.2 Quantitative sensory testing (QST)

The measurement of sensory thresholds to thermal, vibration or mechanical stimulus indicates the loss or gain of function to each sensory modality. Commonly, temperature (cold and warm) detection and pain thresholds are evaluated distally in the dorsum of the hands and feet. At this sites, skin thickness-dependent delay and attenuation of temperature is reduced for contact heating (thermode) in comparison to glabrous skin [39]. Through QST examination we obtain functional information from small and large nerve fibers depending of the sensory modality examined.

One of the most common findings in QST is cold allodynia, that means early pain sensation at low temperatures (range from 10° to 25°C) frequently seen in oxaliplatin treated patients. Moreover, signs of sensory loss are present early in CIPN at hands and feet in comparison to other proximal sites (see an example in **Figure 3b**). Patients show high thresholds for warm and cold detection as well as for hot pain revealing deficient function of small nerve fibers [8, 10, 40].

In addition, the higher vibration and mechanical detection thresholds at upper and lower limbs reported by different authors indicates the coexistence with distal damage at large myelinated sensory fibers [38, 41, 42]. In fact, vibration detection threshold at tip of the big toe was found abnormal earlier than thermal QST [43]. However, QST has also important limitations that should be considered. First, it needs patient's cooperation. Second, a trained examiner should repeat stimuli to ensure consistency of responses. Finally, abnormal thresholds have been reported and considered a subclinical deficit for warm and cold sensations before receiving chemotherapy (at baseline) which makes difficult to detect a significant change related with starting of CIPN [10, 20, 21, 44].

6.3 Study of the autonomic nervous system

To evaluate the presence of dysautonomia, which is a failure of the sympathetic and/or parasympathetic nervous system, it may be possible to record the palmar and plantar sudomotor skin response. This is a change in the voltage measured from the surface of the skin which occurs after emotional or noxious stimuli, or following deep inspiration. The absence of response has been associated to axonal unmyelinated peripheral neuropathies [45]. More recently, the measurement of electrochemical skin conductance (Sudoscan) is an easy-use alternative that could have its role in future studies on CINP [46]. Parasympathetic function is assessed by measuring the variability of the R-R interval of heart's beat by different maneuvers (normal breathing, Valsalva, stand up). It requires more complex neurophysiological setting and the clinical relevance in CINP is still to be investigated.

7. Other non-neurophysiological techniques for early detection of CIPN

Skin biopsy allow us to examine directly under microscopy the free sensory nerve endings at skin. This is a well-recognize technique to quantify axonal damage occurring in sensory fibers with a minimal invasive punch biopsy. It provides support for diagnosing small fiber neuropathy [47] and is considered an early marker of more generalized (large and small) sensory polyneuropathy such us diabetic polyneuropathy. It makes skin biopsy presumably useful for early detection and monitoring patients receiving chemotherapy. Although a significant reduction in intraepidermal nerve fiber density has been reported by some authors after receiving oxaliplatin [42, 48], others have found cutaneous innervation more preserved [49]. In our experience, even when many patients show functional loss of small fibers (higher warm and cold detection thresholds at feet), the intraepidermal nerve fibers density seems to be partially preserved. Indeed, the rationale to less vulnerability of small neurons at DRG or higher capability to reinnervate the terminal small nerve fibers in contrast to myelinated receptors and fibers is still open.

Neuroimage is becoming available in different ways for providing signs of neurotoxicity in CIPN. Information by using these techniques is limited to few studies so far. Nerve high resolution ultrasound served to identify an increase in the cross-sectional area meaning a nerve enlargement at upper and lower limbs in patients receiving oxaliplatin [50] and taxanes [51]. By using magnetic resonance neurography has been also reported a significant hypertrophy of DRG [52] whereas other nerves, sciatic nerve, remain normal. In addition, changes at central nervous system, in dorsal columns at spinal cord, has been reported in patients affected by thalidomide-induced CIPN [53, 54].

Molecular biomarkers may also have a role in early detection of CIPN. They are in different categories, from pharmacogenomics to surrogate markers of

neurotoxicity. Unfortunately, none has been established in clinical practice because of lack of large-scale and validation studies. The majority of genetic variants which has been candidates to indicate higher susceptibility of neurotoxicity showed controversial results (for example, see recent reviews [55, 56]. More is known about other molecules reflecting nerve damage which are available at blood analysis such us neurofilaments. Neurofilament light chain (NfL) is a cytoskeletal neuron-specific protein which has found increased after receiving vincristine and oxaliplatin [57]. Nerve Growth Factor (NGF) levels were also find higher in painful CIPN whereas they remained stable in patients with painless or absent CIPN [49]. Other metabolic parameters such us low hemoglobin or vitamin D levels or higher gamma-glutamyl transferase (GGT) have been identified as independent predictors associated to CIPN [58].

8. When CIPN is supposed to be resolved? Indicators of recovery

This is the main question in patient's mind which is difficult to answer. It depends on many factors, specially the severity of axonal loss at maximum of the neurotoxic effect of the drug. Complete recovery is calculated in about 40% of patients at 8–12 months after discontinuation of oxaliplatin whereas in almost 35% of patients is estimated to be persistent more than 5 years [59, 60]. Lower incidence has been reported for cisplatin which is estimated in 20% of patients at 12 months after therapy [27]. Patients treated with taxanes experience symptomatic sensory neuropathy distally at fingertips in hands and feet. It has been estimated in more than 70% of patients, being persistent in most of them longer than 5 years in some series [61]. Vincristine-induced neuropathy in pediatric population combines sensory and motor symptoms that are persistent in 27% of patients 2 years after treatment [62]. No correlation has been established between time until recovery and any clinical or neurophysiological parameter as far as I know. However, it is possible to said that low amplitudes at sensory nerve action potentials make prognosis for recovery very poor despite intraepidermal nerve fibers are partially preserved (personal observation).

9. Neuroprotection and other recommendations

Neuroprotectants have limited beneficial effects for preventing CIPN. The first step is to modify the chemotherapy regimen, such as dose reduction and longer interval between cycles, especially platinum agents like oxaliplatin or cisplatin and vincristine [63]. This is necessary in approximately 40% of patients based on average from different reports [64].

The intend to reduce oxidative-stress and the up-regulation of pro-inflammatory cytokines due to chemotherapy have led many authors to test antioxidant therapy. This is the case of vitamin B6, vitamin E and alpha-lipoic acid among others. Despite of contradictory results reported until now in different trials (see a recent review, [65]), the easiness to acquire these products for patients and their natural origin, most of them nutritional supplements, makes them a good choice in poor symptomatic CIPN or intermittent therapy between cycles of chemotherapy. Other pharmacological products such as the amifostine, glutathione, calcium/magnesium, minocycline or mangafodipir need further research.

Symptomatic treatment with antiepileptic drugs (pregabalin, gabapentin, oxcarbazepine) or antidepressants (duloxetine, amitriptyline) is recommended at low dose with a progressive increase until partial or total alleviation of sensory symptoms.

Regular exercise and lifestyle interventions help to prevent inactivity and improve body mass index [66]. Regular aerobic exercise training (30 minutes/day or 4 hours/week) and daily walking activity between 8000 to 10000 steps/day during 5 days/week are recommended (see https://www.foundationforpn.org). Indeed, they contribute to sensory and motor rehabilitation, improve self-confidence to walk previously diminished because of sensory loss in CIPN. Sensory feet stimulation with a rubber carpet of different textures as well as hand manipulation of soft tissue or lentils could be a form of manual therapy for neurorehabilitation after receiving chemotherapy treatment. An interdisciplinary team is also recommended to attend needs of persons with CIPN in every oncologic center [67].

10. Conclusion

This chapter reports on clinical assessment of CIPN in such a way to be easily understandable. The number of cancer survivors has been fortunately growing, so complications of neurotoxicity after chemotherapy has become a first order problem for clinicians that are searching a better quality of life for their patients. Mechanisms to produce CIPN are diverse depending of the drug and most of them converge on the same targets. The present manuscript emphasizes a comparison of different type of nerve fibers that lead to a wide spectrum of symptoms, mainly sensory, which are related to axonal damage at different type of nerve fibers. Selective techniques are necessary to detect sensory disfunction which seems to affect early distal vibration and warm perception. No indicators have found to predict patient's recovery so we have to assume that this process is possible, although perhaps partially, in all cases. The future will come to reduce toxic damage by personalized drug plans as well as multidisciplinary professional care to our patients.

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Conflict of interest

The author declares no conflict of interest.

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