short review

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Chemotherapy-induced peripheral neuropathy (CIPN)

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Summary Many cancer patients are cured from their malignant tumor, but may suffer from long-term, chemotherapy-induced peripheral neuropathy. This frequent and often disabling condition results from treatment with anticancer drugs including microtubulin-targeting agents such as taxanes, vinca alkaloids, and some immunotoxins; platinum compounds; certain proteasome inhibitors like bortezomib; and immunomodulatory drugs such as thalidomide. Moreover, immune checkpoint inhibitors can cause an autoimmune-mediated peripheral neuropathy. Neuropathic symptoms include pain, numbness, tingling, or cold hypersensitivity in the hands and feet, as well as motor weakening or disorders of the autonomous nerve system. Medical treatment is often unsatisfactory. First-line options include antidepressants like duloxetine, venlafaxine or amitriptyline, and antineuropathic drugs like gabapentin or pregabalin. In addition, topical therapies with capsaicin or lidocaine have been applied. In severe cases, medication with tramadol or opioids may be required for painful paresthesia. Physiotherapy, sensory integrative occupational therapy, and various physical agents can be helpful. The course of disease, however, is usually protracted, and the symptoms generally gradually decrease. In this short overview, we describe medical and physical treatment options for chemotherapy-induced peripheral neuropathy.

Keywords Neuropathic pain · Paresthesia · Opioids · Physiotherapy · Physical therapies

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Neuropathic symptoms

Patients suffering from chemotherapy-induced peripheral neuropathy (CIPN), also known as polyneuropathy, frequently experience sensory symptoms like tingling, numbness, shooting or burning pain. Sensing of vibration, proprioception, temperature and pinprick may be affected. Some patients report muscle cramps, or sensations like ants crawling under their skin. Approximately 60% of affected CIPN patients report numbness and tingling [1]. Feet and/or toes are more frequently affected than hands and/or fingers. The distribution of CIPN symptoms is usually distal, bilateral and symmetrical like glove and stocking. With increasing numbers of chemotherapy cycles, the affected body sites and the intensity of the symptoms tend to progress from distal to areas that are more proximal. Regression of symptoms is usually slow, and some patients become permanently impaired. In a meta-analysis, the prevalence of CIPN is 68.1% in the first month after chemotherapy, 60.0% at 3 months, and 30.0% at 6 months or more [2]. Axonal neuropathy is common, but demyelinating neuropathy or mixed forms can occur.

In addition, motor weakness, autonomic impairment or cranial nerve involvement are possible [3]. Impaired hand fine motor skills can lead to disability. Autonomic neuropathy may involve dysregulation of heartbeat, blood pressure, intestinal peristalsis, and urinary bladder or erectile dysfunction. A recent analysis has identified four distinct clusters of CIPN, namely the sensory neuropathy symptom cluster, the

motor-sensory neuropathy symptom cluster, the sensorimotor neuropathy symptom cluster, and the autonomic neuropathy symptom cluster [4]. In a systematic review, CIPN was likely associated with poor quality of life of cancer survivors [5].

Platinum compounds lead to two distinct neuropathic symptoms. Acute, transient neurotoxicity is common, which may occur shortly after administration of oxaliplatin, whereas chronic toxicity leads to more persistent impairment [6]. Oxaliplatin causes paresthesia in the extremities but also in the mouth and throat, which includes voice changes, vision changes, pharyngolaryngeal dysesthesia, perioral numbness, pain, muscle spasms, cramps, or tremors [7]. Some patients experience painful hypersensitivity to cold exposure. Chronic CIPN due to platinum-based chemotherapy tends to increase with the number of chemotherapeutic cycles. It can worsen even months after cessation of chemotherapy (so-called "coasting" phenomenon). Moreover, prolonged treatment may affect proprioception, resulting in an ataxic gait [6].

Taxanes cause symmetric distal numbness and paresthesia. Paclitaxel can induce symptoms similar to arthralgia or myalgia. Typically located in the trunk or hip, they may be misjudged as skeletal complaints, but are in fact manifestations of neuropathic pain [8]. These symptoms typically occur after each chemotherapy cycle, peaking at day 2–3 and tend to resolve between cycles.

Vincristine is the most neurotoxic vinca alkaloid as compared with vinblastine and vinorelbine. Distal paresthesia and dysesthesia are characteristic. Muscle weakness can appear in distal muscles of hands and feet. Sometimes focal neuropathy of peripheral or cranial nerves is noticed. Furthermore, more than one third of vincristine-treated patients develop autonomic nervous system dysfunction [3].

The toxic component of immunotoxins may also cause CIPN, which is the most common adverse event in patients receiving brentuximab vedotin [9].

Bortezomib and immunomodulating drugs, thalidomide and lenalidomide, are used for treatment of multiple myeloma. Bortezomib induces sensory loss or paresthesia with pain being the predominant symptom [3]. Bortezomib-associated CIPN is reversible in most cases. Thalidomide causes sensory neuropathy while motor symptoms are rarely seen. Constipation resulting from autonomic neuropathy affects 80–90% of patients [3]. In contrast, lenalidomide rarely causes neuropathy.

Antibody-based treatment with immune checkpoint inhibitors can induce an immune-mediated peripheral neuropathy. Approximately 1% of patients treated with monotherapy, and 2–3% of those treated with combination therapy are affected [10].

Diagnosis

Diagnostic procedures include complete medical history, painDETECT questionnaire [11], clinical assessment including neurological examination, laboratory tests, electrophysiological testing (electroneurography; sometimes electromyography) and quantitative sensory testing. For specific assessment and scoring, the Quality of Life Questionnaire–CIPN 20-item scale module of the European Organization for Research and Treatment of Cancer (EORTC QLQ-CIPN 20) can be utilized [11]. The standard Quality of Life Questionnaire (EORTC QLQ-C30) does not contain specific items for neuropathy.

Dependent on clinical assumptions, laboratory tests may include complete blood count, hepatic and renal function panel, folic acid, vitamin B12, fasting blood glucose, iron status and thyroid-stimulating hormone levels, parameters of inflammation and autoimmune disease, serum and urine free light chain assay. Analysis of cerebrospinal fluid, or biopsies of nerves, muscles or skin may be required.

Differential diagnoses

Other drugs may cause neuropathy, e.g., metronidazole, nitrofurantoin, linezolid and isoniazid; antifungal triazole drugs; nucleoside reverse transcriptase inhibitors; levodopa; amiodarone, and statins [12]. The most frequent causes of neuropathy in Central Europe are diabetes and alcohol. Polyneuropathy can occur as a paraneoplastic phenomenon, mainly in multiple myeloma and amyloidosis. Furthermore, exposure to heavy metals, autoimmune disease, e.g., vasculitis, and infections like acquired immunodeficiency and Lyme disease are possible causes. Combinations of causes are conceivable, and pre-existing polyneuropathy may worsen the chemotherapy-related complaints.

Medical treatment

The benefit of medical treatment is unsatisfactory, and no single drug can warrant relief of CIPN-related pain. Duloxetine, a selective serotonin–noradrenalin reuptake inhibitor (SNRI), reduced oxaliplatin-related neuropathic pain in a randomized, placebo-controlled trial [13, 14]. The use of venlafaxine (another SNRI); tricyclic antidepressants like amitriptyline; furthermore gabapentin or pregabalin can be considered whereas lamotrigine is discouraged in guidelines [15]. Gabapentin and pregabalin are anticonvulsant drugs used for treatment of neuropathic pain. Tramadol, a weak opioid which also inhibits noradrenergic and serotoninergic reuptake, thus displaying an antidepressant action, is a useful option. Furthermore, topical treatment of neuropathic pain with capsaicin 8% patch (Qutenza®, Grünenthal, Germany) or lidocaine 5% medicated plaster (Versatis®, Grünenthal,

Table 1 Treatment options for neuropathic pain

First-line treatment options	Duloxetine 60–120 mg [15, 26]
	Gabapentin 1200–3600 mg [16]
	Pregabalin [16]
	Other SNRIs, e.g., venlafaxine 150–225 mg [15, 16]
	Amitriptyline, tricyclic antidepressants [15]
Second-line treatment options	Capsaicin 8% patches [16]
	Lidocaine 5% patches [16]
	Tramadol [16]
Third-line treatment options	Strong opioids [16]

Germany) can be administered [16]. If other options are unsuccessful, neuropathic pain maybe controlled by opioids [15]. In addition, a topical treatment with 1% menthol cream might be useful in some cases [17].

Based on a systematic review and meta-analysis, a general algorithm for the treatment of neuropathic pain is provided [16]: For first-line treatment, SNRIs like duloxetine and venlafaxine are recommended; furthermore pregabalin and gabapentin; as well as the antidepressant amitriptyline. Tramadol, lidocaine or capsaicin patches are second-line options; and strong opioids such as morphine and oxycodone are third-line options. An overview on treatment options available in Central Europe is provided in Table 1.

Physical treatment modalities

From the field of physical medicine, there are different physical modalities which are individually prescribed and administered to mitigate CIPN symptoms [20, 21]. These physical agents are part of a traditional, experienced-based medicine approach [20, 21]. Most of these physical modalities are applied to reduce chronic pain, severe dysesthesia, and peripheral dystrophy [18–21]. In the treatment of CIPN, they have empirically shown benefits when applied in a multimodal setting [18–21]. Furthermore, these modalities show fewer side effects than drug-based treatment [18–21]. Nevertheless, many of these physical modalities currently lack strong scientific evidence in the treatment of CIPN [18–21]. These physical agents are components of electrotherapy, balneology, thermotherapy, and of mechanotherapy [18–25].

Electrical therapy can be applied as low-frequency electrical therapy in the form of galvanic baths, and (low-frequent) transcutaneous electrical nerve stimulation. The so-called "Hochtontherapie" is a special middle frequency therapy [18, 19].

Carbon dioxide (CO_2) baths are a typical balneological modality, while special massages such as lymphatic massage and compression are both mechanotherapies with the intention to counteract CIPN symptoms. From thermotherapy, cryotherapeutic approaches seem to be quite helpful [18–21].

At the moment, CIPN is recommended as a so-called exceptional indication or expert indication ("off-label use") for the treatment with focused extracorporeal shockwave treatment (fESWT) [22–25]. FESWT seems to be effective (personal observation), and is a time- and cost-efficient approach [22–25]. By using fESWT, mechanotransduction seems to be the therapeutic principle, and the treatment goals are pain reduction, neuroregeneration, and angioneogenesis [22–25]. In our opinion, future research should focus on effects and efficiency of fESWT in the treatment of CIPN, especially in a combined approach with exercise.

More active physical modalities such as physiotherapy, occupational therapy, immersion (water therapy), and especially medical exercise are strategies with the intention to improve sensorimotor functions of upper and lower limbs, flexibility, endurance capacity, and of muscular strength [18–21].

Prevention

The most relevant measure in prevention of CIPN is the adjustment of chemotherapy if possible. Oncologists should identify whether dose reduction, termination of chemotherapy, or change to drugs that do not cause CIPN may be appropriate.

Medical prevention of CIPN has not been successful despite numerous trials. The S3-guideline of supportive therapy of oncological patients, and the ASCO guideline do not recommend the use of drugs, e.g., calcium/magnesium, amitriptyline, carbamazepine, gabapentin/pregabalin, cannabinoids, glutamate, amifostine, glutathione, N-acetylcysteine, alpha-liponic acid, venlafaxine, and vitamins B or E [15, 26]. Moreover, the use of acetyl-l-carnitine is explicitly discouraged as the harms outweigh benefits [26].

There have been several attempts of prophylaxis by physical measures. A Danish study reported reduced docetaxel-associated CIPN using distal-extremity cryotherapy with frozen gloves and socks [27]. Initial encouraging reports seemed to support this approach, but a recent multicenter randomized controlled trial failed to confirm a statistical improvement [28]. Compression therapy has been tried with a tight surgical glove on one hand during taxane infusion [29]. On the intervention hand side, grade ≥2 sensory neuropathies were observed in 21% as compared with 76% in hands that were not gloved. While this is an interesting observation, the number of patients in this study is too small to draw definite conclusions.

Exercise appears to be effective in reducing the occurrence of CIPN. In a large randomized trial, a moderate-intensity, home-based, walking and resistance exercise program significantly reduced CIPN symptoms of hot/coldness in hands/feet [30]. Numbness and tingling were also reduced albeit significance was not reached. Conversely, electro-acupuncture

failed to improve CIPN in a randomized trial [31]. Of concern, patients treated with acupuncture showed a slower recovery than the control group that had obtained sham treatment.

In conclusion, medical prophylaxis of CIPN has not been successful. While the current evidence is not yet sufficient for a general recommendation [26], exercise, compression therapy and cryotherapy appear to be promising treatment options and merit further attention.

Take home messages

Chemotherapy-induced neuropathic pain is treated with antidepressants; pregabalin/gabapentin; lidocaine or capsaicin patches; or opioids in combination with physical treatment modalities. For prevention, dose reduction of modification of chemotherapy should be considered. While medication for prophylaxis is ineffective, physical measures including exercise might help reduce the development of CIPN.

Conflict of interest T. Licht, M. Keilani and R. Crevenna declare that they have no competing interests.

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