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Summary

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent and disabling side effect. They have a limiting effect on the dose and duration of chemotherapy, representing a loss of opportunity for the patient. The intensity of symptoms depends on the patient's genetic predisposition. There is no recommended preventive or curative treatment.

There are no clinical studies evaluating the value of homeopathic treatment. Only one expert recommendation has been published on the prevention of NPCI. Preventive treatment is essential, because once NPCI has set in, it requires long treatments of uncertain efficacy.

Based on the pathophysiology of oxaliplatin and paclitaxel neurotoxicity, toxicology and computerized symptom indexing, a list of 14 preventive and curative drug candidates is presented, along with their key symptoms. The choice of drug(s) will be made according to the principle of symptom individualization specific to the homeopathic method.

For preventive treatment, **Phosphorus**, **Arsenicum album**, **Rhus toxicodendron**, **Oxalicum acidum** and **Sulfur**, combined with **Nerfs 4CH** or- ganotherapy, represent the 5 most frequently indicated drugs.

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In curative treatment, for late sequelae, **Secale cornutum**, **Lycopodium clavatum**, **Nux vomica**, **Silicea** and **Natrum muriaticum** can be added to the above-mentioned drugs. Because of the organic damage to the neurons, these treatments need to be continued for a long time. Alternate prescriptions of the most "similar" drugs are possible, in an attempt to determine with the patient which is most effective. Integrative management is recommended to maximize the effect of homeopathic treatment. This preliminary theoretical work can serve as a basis for future clinical studies.

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) are a common and disabling side effect. They have a limiting effect on the dose and duration of chemotherapy, representing a missed opportunity for the patient. The intensity of symptoms depends on the patient's background and genetic predisposition. There is no recommended preventive or curative treatment.

There is a lack of clinical study evaluating the benefits of homeopathic treatment. Only an expert recommendation has been published for the prevention of CIPN. Preventive treatment is essential because once established, CIPN requires lengthy and inconsistently effective treatments.

Based on the pathophysiology of neurotoxicity with oxaliplatin and paclitaxel, toxicology, and computerized symptom repertory, a list of 14 candidate homeopathic medicine for preventive and curative purposes is presented with their key symptoms. The choice of one or more drugs will be made according to the principle of individualization of symptoms specific to the homeopathic method.

In preventive care, **Phosphorus**, **Arsenicum album**, **Rhus toxicodendron**, **Oxalicum acidum**, and **Sulfur**, combined with organotherapy **Nerves 4c**, are the five most frequently recommended medicines.

For curative purposes, in the case of late sequelae, **Secale cornutum**, **Lycopodium clavatum**, **Nux vomica**, **Silicea** or **Natrum muriaticum** can be added to the previously mentioned medications. Treatments should be conducted for an extended period due to the neuronal organic involvement. Alternating prescriptions of the most "similar" medicines are possible to determine, along with the patient, which one is the most effective. Integrative care is recommended to enhance the action of homeopathic treatment. This preliminary theoretical work can serve as a foundation for the development of upcoming clinical studies.

Key words: homeopathy, chemotherapy-induced peripheral neuropathy, integrative oncology, oxaliplatin, paclitaxel
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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) represents a therapeutic problem for patients and caregivers alike. Their incidence varies between 30 and 90% depending on the chemotherapy regimen, and after hematological toxicity, they are the 2nd limiting factor of chemotherapy [1]. The exact mechanisms behind the development of these neuropathies are not fully understood, and there is no known effective preventive or curative treatment [2].

Several chemotherapies are neurotoxic: platinum salts (mainly oxaliplatin, and to a lesser extent cisplatin and carboplatin), spindle poisons (mainly paclitaxel, but also docetaxel, cabazitaxel and erlotinib); Madagascar periwinkle alkaloids (especially vincristine, vinorelbine, vindesine and vinblastine) and bortezomib, a targeted therapy [3].

NPCI is responsible for an altered quality of life and a loss of opportunity for patients due to premature cessation of treatment. They also represent a significant financial burden for society.

There are no clinical studies evaluating the use of homeopathy in this indication [4]. Only one expert recommendation has been published by the Homeopathic Society.

International Supportive Care in Oncology (SHISO) [5]. The aim of this article is to present the most frequently indicated candidate drugs for both preventive and curative treatment. The secondary objective is to help the reader make the most effective individualization and prescribing possible.

Methodology

Our approach is based on the pathophysiology of NPCI with oxaliplatin and paclitaxel. We will study clinical symptomatology, toxicology, medical literature and electronic symptom indexing to identify the most convincing drug candidates.

Pathophysiology

The dose of chemotherapy, the duration of treatment and the patient's genetic predisposition increase the risk of developing chemo-induced peripheral neuropathy [6]. Oxaliplatin generates apoptosis in the spinal ganglion through the formation of adducts on nuclear DNA. It also generates a negative interaction with mitochondrial DNA. **Oxalate** production is responsible for axonal ion channel dysfunction. Other lesions result from oxidative stress triggered by the release of pro-inflammatory cytokines (IL-6, IL-8, IL1 β , TNF- α). These lead to sensitization of nociceptors, axonal degeneration and deregulation of voltage-gated calcium channels at the nodes of Ranvier. Toxicity is also suspected in the blood-nerve barrier represented by the vasa nervosum, favoring neuronal dysfunction and neuroinflammation leading to late sequelae [3,6].

Taxanes and spindle poisons inhibit the depolymerization of microtubules, and hence the formation of the mitotic spindle during cell division in cancer cells. Excessive microtubule formation disrupts axonal transport. This, in turn, alters mitochondrial function, leading to a cellular energy deficit and loss of axon integrity, which can lead to axon degeneration. The release of pro-inflammatory cytokines is also involved [3,6].

Symptomatology

NPCI follow a "gloves" and "socks" pattern, with symptoms of increasing severity:

- Allodynia: pain provoked by a stimulus that is not normally painful.
- Paraesthesia, which is a spontaneous or provoked abnormal sensation that cannot be removed, such as tingling or pins and needles.
- Dysesthesia, which is a disagreeable abnormal sensation, spontaneous or provoked, with piquenching or burning pain.

If pain worsens, it can lead to the onset of motor symptoms (tetanic spasms, fasciculations) and comorbidities such as anxiety, depression, sleep disorders, falls and sprains.

The DN4 questionnaire is used to quantify neuropathic pain. A score greater than or equal to 4 out of 10 is considered positive [7]. Symptoms are also graded from 1 to 4 [8]. Grade 1 calls for protective measures, grade 2 for dose reduction, grade 3 for temporary or permanent discontinuation of chemotherapy, and grade 4 for specialized treatment.

Oxaliplatin neuropathy (Folfox, Folfirinox, Flot protocols)

They occur in 90% of patients immediately after chemotherapy infusion, and are triggered by cold. They last a few days, then subside or even disappear before the next chemotherapy treatment. Patients are strongly advised to avoid touching cold, breathing cold air or drinking cold fluids. Pain on chewing and cramping may occur, as well as slurred speech.

Taxane neuropathy: Taxol, Carbo-Taxol or Taxotere-Cyclophosphamide protocol

The prevalence of symptoms ranges from 59 to 87% of patients. They include quadridistal paresthesia with a sensation of numbness (in 100% of cases), tingling (80%), hypersensitivity to cold (60%) or neuropathic pain (50%). Half of patients suffer from loss of balance due to impaired reflexes and proprioception.

There is no curative treatment: only stopping or reducing chemotherapy is therapeutic. The application of refrigerated bracelets and boots before and during the session is a real preventive measure.

Homeopathic treatment

Systematic cataloguing of the specific symptoms of NPCI (Fig.1) [9], toxicology and pathophysiology point to 14 candidate drugs:

- | | |
|------------------------------|---------------------------------|
| 1. <i>Arsenicum album</i> | 8. <i>Lycopodium clavatum</i> |
| 2. <i>Phosphorus</i> | 9. <i>Nux vomica</i> |
| 3. <i>Causticum</i> | 10. <i>Silicea</i> |
| 4. <i>Sulfur</i> | 11. <i>Natrum muriaticum</i> |
| 5. <i>Rhus toxicodendron</i> | 12. <i>Aconitum napellus</i> |
| 6. <i>Oxalicum acidum</i> | 13. <i>Carboneum sulfuricum</i> |
| 7. <i>Secale cornutum</i> | 14. <i>Thallium sulfuricum</i> |

Of the various pathophysiological mechanisms, we mention *Phosphorus* for its anti-inflammatory action, *Oxalicum acidum* for its anti-oxalate action and *Secale cornutum* for its tropism on the *vasa nervosum*.

Toxicology: *Arsenicum album*, *Phosphorus* and *Thallium sulfuricum*.

The repertory includes *Arsenicum album*, *Rhus toxicodendron*, *Sulfur*, *Silicea*, *Causticum* and *Phosphorus*.

In practice, we need to differentiate between preventive treatment, carried out during chemotherapy, and curative treatment, carried out after chemotherapy, in the management of late sequelae.

Preventive treatment

Follow SHISSO recommendations [9]:

- *Nerfs 8DH* or *4CH*, 1 ampoule drinkable in a little water, keep a little in the mouth before swallowing, morning and evening at D-1, D0, D1, D2 and longer if tingling persists;
- *Phosphorus 15CH*, 3 granules in the evening at D-1, D0, D1, D2 and longer if tingling persists;
- *Oxalicum acidum 9CH* 3 granules morning at D-1, D0, D1, D2 in case of chemotherapy containing oxaliplatin.

This treatment can, of course, be modified and adapted according to the patient's symptoms. *Phosphorus* can then be replaced by *Arsenicum album* or *Rhus toxicodendron*, depending on the patient's general signs, modalities and concomitant symptoms ([10]).

Curative treatment

The first question to ask the patient concerns thermal modalities. NPCI are initially aggravated by cold and improved by heat, indicating *Arsenicum album* (sensation of thick soles, impression of walking on wood), *Phosphorus*, *Rhus toxicodendron* and *Causticum* (general weakness with weight loss, joint stiffness with muscular atrophy, contraction of flexors and ankylosis, paresis or paralysis of isolated territories: face, larynx, sphincters... aggravated by dry cold).

This pattern may be reversed after a few months, when the condition becomes chronic. Patients are then aggravated by the heat and seek out the cold. They feel better walking barefoot on cold tiles, and put their feet out of bed when they sleep. This indicates *Sulfur*, but also *Secale cornutum*. The latter is better known for its indication in arterial pain. Yet its characteristic symptoms correspond to NPCI. The patient describes burning, stinging pain improved by cold, a sensation of electric current in the extremities; hyperesthesia to the touch of fingers and toes; a sensation of numbness or tingling of the soles of the feet aggravated by walking or standing.

During the inventory, the patient will be asked to specify the precise location of the injury in the upper limb (hand, finger or fingertips) or lower limb (foot, sole of foot or toes). The type of sensation is also important: numbness, tingling, tingling or burning.

We systematically add the heading "inflammation of the nerves", and ask the patient if objects frequently fall out of his or her hands (heading: clumsiness, dropping, etc.).

things in the hands) and if he/she has imbalances when walking (heading: stumbling when walking, clumsiness of limbs). Individualization through electronic indexing makes it easier to identify the drug(s) most "sem- blable" to the patient's specific neuropathic symptoms. The addition of mental symptoms, where they exist, clarifies the choice of medication.

Prescribing the isotherapeutic **Nerfs 4CH** is highly effective in prevention, but much less so in chronic treatment. It is, however, worth trying for the first month. To increase its effectiveness, it is sometimes necessary to take more doses during the day. To do this, I recommend that patients put a drinkable ampoule in half a glass of water, dynamize the mixture by swirling it about fifty times with a teaspoon, and then take a teaspoon several times a day.

I often use the N-of-1 experimentation technique applied to homeopathy [11]. We prescribe in 9CH the 3 medicines that seem most "similar". Three morning and evening granules of the first drug until the tube is empty (about 12 days). The patient stops all treatment for 2 days, then starts again with the second drug, following the same procedure, then does the same with the third drug. The patient is asked to rate neuropathic pain from 1 to 10 at the start of each tube. The patient is reviewed after two cycles of this treatment (3 months). If improvement is observed, the patient is continued on the drug(s) that gave the best therapeutic results, gradually increasing the dilutions over the months. In the event of failure, the case is reviewed, new symptoms are sought and 3 other drugs are prescribed using the same technique.

The patient should be warned that treatment will take a long time, even with the right choice of medication. This is a pathology

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and regrowth of myelin sheaths, when still possible, is very slow.

It is important to adopt an integrative approach [12]. Homeopathic treatment can be combined with pregabalin, gabapentin or duloxetine. Whenever possible, acu-puncture, reflexology, osteopathy and micronutrition can also be combined [4]. Specialized physiotherapists play an important role, with walking courses on different types of pavement and learning to self-wipe palms and soles with pimples.

Conclusion

We emphasize the importance of preventive treatment of neuropathies, using the SHISSO recommendation for any chemotherapy involving oxaliplatin, paclitaxel or vincristine. In chronic cases, the individualization of symptoms will enable us to determine the most similar candidate drug(s), which should be prescribed over several months, with treatment adaptation often necessary in the choice of drug and its dilution. **Phosphorus**, **Arsenicum album**, **Causticum** and **Sulfur**, once individualized, are often the most useful.

Links of interest

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