Chemotherapy induced peripheral neuropathy. Case reports

Neuropatia periférica induzida pela quimioterapia. Relato de casos

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RESUMO

JUSTIFICATIVA E OBJETIVOS: A neuropatia periférica induzida por quimioterapia (NPIQ) é um efeito adverso comum relatado por pacientes sob terapêutica antineoplásica e pode afetar o sucesso do tratamento, os resultados e a sua qualidade de vida. A NPIQ começa com alterações sensoriais progressivas simétricas das mãos e dos pés, em distribuição em meia e luva. Atualmente, não existe tratamento ou terapêutica preventiva para a NPIQ.
RELATO DOS CASOS: Este estudo representa a atividade da Unidade Multidisciplinar de Dor do Hospital Santa Maria em Lisboa entre 2018 e 2023, especificamente em pacientes oncológicos com NPIQ. No total, esta unidade observou 57 pacientes, 43,9% tinham câncer do cólon/reto, 28,1% hematológico, 21,1% de mama, 3,5% gástrico, 1,8% câncer do ovário e 1,8% pulmão. O fármaco quimioterápico mais utilizado foi a oxaliplatina (40,4%), seguida pela capecitabina (24,6%) e paclitaxel (22,8%). A combinação de fármacos quimioterápicos mais prescrita foi capecitabina com oxaliplatina (CAPOX) (22,8%). A unidade multidisciplinar, em conjunto com o departamento de oncologia, estabeleceu um novo procedimento, no qual os pacientes que recebem quimioterapia com um dos agentes conhecidos ligados à NIPQ usaram um par de luvas e meias geladas. 3 pacientes foram submetidos a este método de prevenção e nenhum dos pacientes referiu sintomas de NPIQ.
CONCLUSÃO: O presente estudo contribuiu para alertar para esta doença importante e limitante, e reunir evidências sobre medidas preventivas que reduzem a incidência de NPIQ.
Descritores: Doenças do sistema nervoso periférico, Dor, Qualidade de vida, Quimioterapia.

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HIGHLIGHTS
• Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of chemotherapy, most frequently with oxaliplatin, capecitabine, and paclitaxel.
• CIPN treatment (SSRI's or gabapentinoids) has short scientific validation and its efficacy is limited.
• Frozen gloves and socks could prevent CIPN.

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ABSTRACT

BACKGROUND AND OBJECTIVES: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect reported by patients receiving cancer treatment, and it can affect treatment success, patient outcomes, and quality of life. CIPN typically begins with symmetrical progressive sensory alterations of the hands and feet in a stocking-gloving distribution. Currently, there is no standard treatment or intervention for the prevention, mitigation, or management of CIPN.
CASES REPORT: This study represents the activity of the Pain Multidisciplinary Unit of Hospital Santa Maria in Lisbon from 2018 to 2023, specifically on oncologic patients with chemotherapy-induced peripheral neuropathy. In total, this unit observed 57 patients, 43.9% had colon/rectum cancer, 28.1% hematological, 21.1% breast, 3.5% gastric, 1.8% ovarian and 1.8% lung. The most frequent chemotherapeutic agent used was oxaliplatin (40.4%), followed by capecitabine (24.6%) and paclitaxel (22.8%). The most prescribed combination of chemotherapy agents was capecitabine with oxaliplatin, according to the CAPOX protocol. The multidisciplinary unit, in conjunction with the oncology department, has set a new procedure in which patients receiving chemotherapy with one of the known agents linked with CIPN wear a pair of frozen gloves and socks. Three patients have undergone this prevention method, none of the patients has reported symptoms of CIPN.
CONCLUSION: This study contributes to draw attention to this important and limiting condition, and it also contributes to gather evidence on preventive measures that reduce the incidence of CIPN.
Keywords: Chemotherapy, Pain, Peripheral nervous system diseases, Quality of life.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect reported by patients who are recei-

ving cancer treatment, and it can lead to dose limitation, affect treatment success, patient outcomes and their quality of life[1-3], as it may interfere with pharmacological decisions to continue, modify, delay or stop treatment[1]. Furthermore, CIPN can increase healthcare costs and resource consumption/utilization[3]. In most patients, recovery is, in general, partial with residual deficits[4]. The diagnosis of CIPN remains as an exclusion diagnosis, mainly based on the patient's history[5].

The clinical presentation of CIPN typically begins with symmetrical progressive sensory alterations of the hands and feet (in a stocking-gloving distribution), including paraesthesia, hyperesthesia, hypoesthesia, dysesthesia, or allodynia, including tingling, numbness, impairment of fine motor tasks, and alterations in sensation of touch[1-3].

Currently, there is no standard treatment or intervention for the prevention, mitigation, or management of CIPN[1,2]. The aim of this article was to study the population of cancer patients of Hospital de Santa Maria referred to the Pain Multidisciplinary Unit who exhibited signs and symptoms of CIPN, to raise awareness of the importance of early diagnosis, to try to minimize further damage.

CASES REPORTS

This case report represents the activity of the Pain Multidisciplinary Unit of Hospital Santa Maria in Lisbon from 2018 to 2023, specifically on oncologic patients with chemotherapy induced polyneuropathy referred to the unit (64 patients). This study excluded all patients whose diagnosis of CIPN wasn't verified and all patients who didn't maintain follow-up (at least one evaluation after institution of therapeutics).

In total, the unit observed 57 patients with symptoms compatible with neuropathic pain or neuropathic altered sensations that started after a chemotherapy session, within the period mentioned above (according to the DN4 questionnaire).

Information about the oncologic diagnosis, prescription of chemotherapy, neuropathic symptoms, and prescription of treatments were collected. All the data were analyzed with SPSS Statistics 29. Considering that the unit is included in a University Hospital, all the patient's data are dismissed from Free Informed Consent Term (FICT), assured the anonymity of the data.

RESULTS OF THE GENERAL SAMPLE

The average age of the sample was 62.6 years old, with a standard deviation of 11.7 years. Almost two thirds of the sample were women (63,2%). The summary of their oncologic diagnosis is stated in table 1. The most frequent chemotherapeutic agent used was oxaliplatin (40.4%). followed by capecitabine (24.6%) and paclitaxel (22.8%). The most prescribed combination of chemotherapy agents was capecitabine with oxaliplatin (CAPOX) (22.8%). The summary of the chemotherapy agents used is stated in table 2.

Table 1. Summary of oncologic diagnosis

	Frequency	%
Colon/Rectum	25	43.9
Hematological	16	28.1
Breast	12	21.1
Gastric	2	3.5
Ovarian	1	1.8
Lung	1	1.8

Table 2. Summary of the chemotherapy agents used

	Frequency	%
Doxorubicin	4	7.0
Idarubicin	2	3.5
Cyclophosphamide	4	7.0
Ifosfamide	1	1.8
Paclitaxel	13	22.8
Docetaxel	3	5.3
Vincristine	4	7.0
Carboplatin	4	7.0
Oxaliplatin	23	40.4
Cisplatin	3	5.3
Cytarabine	1	1.8
Capecitabine	14	24.6
Folinic acid	9	15.8
5-Fluorouracil	10	17.5
Lenalidomide	6	10.5
Thalidomide	2	3.5
Bortezomib	1	1.8
Arsenic trioxide	2	3.5

Most of the patients presented neuropathic symptoms in both hands and feet (36 patients – 63.2%), followed by only feet (19 patients – 33.3%). Only 2 patients (3.5%) presented neuropathic symptoms exclusively on their hands. The summary of the prescribed therapy is stated in table 3.

Table 3. Summary of the prescribed treatment

	Frequency	%
Duloxetine	25	43.9
Pregabalin	22	38.6
Gabapentin	25	43.9
Tapentadol	6	10.5
Tramadol	1	1.8
Buprenorphine	3	5.3
Amitriptyline	4	7.0
Capsaicin patches	33	57.9
Lidocaine patches	2	3.5
Acupuncture	4	7

RESULTS ACCORDING TO THE NEOPLASTIC DIAGNOSIS CONCERNING THE CHEMOTHERAPY AGENTS ADMINISTERED AND THE SYMPTOMS DEVELOPED CONSEQUENTLY

Colon/rectum cancer

The chemotherapy agents most frequently administrated were the platinum agents (88%; oxaliplatin – 84%/cisplatin – 4%), followed by folinic acid and 5-fluorouracil (36% each). Residually, 8% of these patients were administered paclitaxel. In concordance with the general sample, 72% had neuropathic symptoms on both hands and feet.

Hematological cancer

The chemotherapy agents most frequently administrated were imunomodulatory agents (lenalidomide – 37,5%/thalidomide – 12,5%), followed by vinca alkaloids (vincristine 25%), antricilines (doxorubicin 12,5%/idarubicin 12,5%), alkylating agents (cyclophosphamide 12,5%/ifosfamide 6,3%) and platinum agents (carboplatin 6,3%/cisplatin 6,3%). Residually 6,3% of these patients were treated with cytarabine. 56,3% had neuropathic symptoms on both hands and feet, 43,8% had neuropathic symptoms on their feet.

Breast cancer

The chemotherapy agents most frequently administrated were the taxanes (91.7%; paclitaxel – 75%/docetaxel – 16.7%), followed by doxorubicin, cyclophosphamide and carboplatin (16.7% each). In concordance with the general sample, 66.7% had neuropathic symptoms on both hands and feet.

Gastric cancer

Only 2 patients of the sample were diagnosed with gastric cancer. One was treated with a combination of paclitaxel, oxaliplatin and capecitabin, presenting neuropathic symptoms on both hands and feet. The other was treated with docetaxel, oxaliplatin and 5-fluorouracil, presenting with neuropathic symptoms only on the feet.

Lung cancer

The one patient in the sample presenting lung cancer was treated with cisplatin, presenting with neuropathic symptoms on the feet.

Ovarian cancer

Only one patient with ovarian cancer integrated the sample, and they were treated with paclitaxel and carboplatin, presenting symptoms on the feet.

Prevention with cryotherapy

Besides treating patients with CIPN, the multidisciplinary unit, in conjunction with the oncology department, had set a new procedure since 2023, in which patients receiving chemotherapy with one of the known agents linked with CIPN had to wear a pair of frozen gloves and socks. This cryotherapy starts 15 minutes before the infusion of the chemotherapy agent, stays during the infusion, with change of gloves and socks to keep the extremities cold, and it's taken off 15 minutes after the end of infusion.

So far, 3 patients (apart from the 57 patients of this sample) have undergone this prevention method, one with breast cancer, one with lymphoma and one with colon cancer, with ages ranging from 35 years old to 55 years old. The chemotherapy agents used were paclitaxel, adriamycin, bleomycin, vinblastine, dacarbazine, capecitabine and oxaliplatin. None of the patients has referred symptoms of CIPN.

DISCUSSION

CIPN is a condition that results from damage to the peripheral nervous system and dorsal root ganglia neurons secondary to the administration of a chemotherapy agent[1,5]. Disruption of axoplasmic microtubule mediated transport, distal axonal degeneration, and direct damage to the sensory nerve cell bodies of the dorsal root ganglia (DRG) are some pathological findings found in individuals with CIPN.

DRG and peripheral axons lack an efficient neurovascular barrier, which allows the facile diffusion of chemotherapy agents in the interstitial surrounding the DRG and along the axon filaments. In addition, capillary fenestrations in the vascular supply to the DRG and axons contribute to the facile diffusion of the chemotherapy agents to the nerve cells[1].

Six mechanisms of peripheral nerve injury have been described in relation to peripheral neuropathy, including metabolic dysregulation, covalent modification, organelle damage (mitochondrial and endoplasmic reticulum damage), intracellular inflammatory signaling (linked to organelle damage and apoptotic death of the neuronal cell), axonal transport defects (via interactions of micro-tubule depolarization), and channelopathies (microtubule polymerization interference and subsequent calcium channel dysregulation)[5].

Distal axonopathy is the most common clinical presentation of CIPN and it is characterized by progressive distal symmetrically distributed symptoms of numbness, tingling, burning, decreased or altered sensation, or increased sensitivity that may be painful in a stocking-glove distribution weeks to months after the administration of a chemotherapy agent. Concurrent loss of deep tendon reflexes in the affected extremities with sensory deficits is an important diagnostic sign associated with greater neurosensory damage[1,4].

When severe, these symptoms commonly cause functional impairment of important activities of daily living such as being unable to walk, button clothing, drive, type, or write[1]. This condition commonly progresses with additional chemotherapy treatments and may eventually become persistent between treatment cycles or with the passage of time. 50 to 60% of patients undergoing chemotherapy will develop CIPN[4,5]. The development of this type of toxicity may result in treatment delays, dose modifications or discontinuation of treatment, which may adversely affect the patients' outcome[1].

CIPN must be differentiated from the symmetrical distal neurosensory manifestations that are associated with paraneoplastic sensory neuropathy or diabetic neuropathy[4]. A baseline and ongoing clinical evaluation (before every cycle) of physical function is a critical but often overlooked aspect, as no biomarker has proven useful for diagnosing and monitoring CIPN[4]. There are

Table 4. Summary of chemotherapy agents associated with CIPN[5]

	Incidence	Malignancy	Manifestations
Vinca Alkaloids	All grade up to 96%. Severe: up to 37%.	Hematologic, lymphatic, and gynecologic malignancies, as well as solid tumors.	Vincristine is associated with the greatest incidence of neurotoxicity. It manifests in the distal lower extremities and progresses proximally, with decreased touch, vibration, and temperature sensations as well as paresthesia and diminished deep tendon reflexes.
Platinum	30% to 40%.		Accumulation in the dorsal root ganglion. Risk relates to higher cumulative dosing, and a "coasting" phenomenon may be observed as effects tend to worsen in the months after stopping treatment.
Bortezomib and Thalidomide	Bortezomib: 37%- 64%. Thalidomide: 23%- 70%.	Hematological.	Thalidomide is characterized by prominent paresthesia in the hands and feet along with numbness and mild motor dysfunction. Bortezomib presents distal paresthesia and numbness especially in the lower limbs, along with sharp or burning pain in the feet.
Epothilones	15%-64%	Breast and prostate.	Predominantly sensory and cumulative symptoms.
Arsenic Trioxides	2%-42%	Acute promyelocytic leukemia (APL).	Mild and reversible, but sensory and motor polyneuropathy has been observed chronically.
Taxanes	30% as monotherapy, 70% when combined with platinum.	Ovarian and breast cancer.	Primarily a sensory neuropathy, severe cases have included motor deficits. Lower dose and in combination with carboplatin for treatment of ovarian cancer reduced the incidence to 6%.

several chemotherapy agents associated with the development of CIPN. Table 4 summarizes the list of the chemotherapy agents known to be associated with CIPN[2,5].

Treatment approaches focus on reduction or relief of neuropathic pain, with early pain management being of utmost importance

Duloxetine is the first line of treatment, having the best scientific validation. Venlafaxine has also been shown to be effective in a small randomized trial[4].

Pregabalin, gabapentin or tricyclic antidepressants may have the potential for symptom control, being a reasonable option if duloxetine has failed or contraindications are present[4].

Opioids can also be used to treat the neuropathic pain but there are no compelling data to suggest that one opioid is better than another. Nevertheless, there are no data supporting the benefit of nonsteroidal anti-inflammatory drugs and glucocorticoids in the setting of CIPN[4].

Capsaicin containing patches (8%) may be considered and are an alternative for oral drugs. Menthol also showed substantial pain relief with minimal toxicity and should be considered as the cost is low and no adverse events have been reported[4].

Topical baclofen/amitriptyline/ketamine showed a non-significant symptomatic improvement[4].

Physical exercise and functional training reduce CIPN symptoms. Training to improve coordination, sensorimotor and fine motor function should begin with the onset of manifest CIPN but can be started earlier[4].

Acupuncture showed insufficient evidence to support or refute its use[4].

There aren't preventive measures with strong scientific evidence. Nevertheless, cryotherapy with frozen socks or gloves showed some promising results in small studies. In a large, randomized phase III study, no difference in CIPN was found, but some neuropathy symptoms were reduced[3,4].

Calcium/Magnesium (Ca/Mg) infusions have been studied for the management of the acute form of oxaliplatin-induced peripheral neuropathy[1]. The results indicated that the Ca/Mg-treated patients achieved a higher cumulative oxaliplatin dose, experienced fewer treatment discontinuations for neurotoxicity, had a lower incidence of oxaliplatin-induced CIPN, a lower incidence of laryngopharyngeal dysesthesia, less grade 3 neurotoxicity, and a greater likelihood of treatment durations greater than 9 months compared to the untreated patient population[1]. In other studies, the limited data are not convincingly positive in favor of Ca/Mg neuroprotection and the overall efficacy results are promising but inconclusive[6].

In the case of vitamin supplementation, vitamins B and E have the broadest support in the literature[7]. All vitamins from the B group function as coenzymes in several intermediary metabolic pathways, including neurotransmitter synthesis and neuronal membrane synthesis. Deficiency of vitamins from B group, especially B12, is known to cause neuropathies, usually accompanied by paraesthesia, numbness, and ataxia[7].

Vitamin E is also often regarded as a treatment option for several neuropathies, such as diabetic neuropathy[7]. Although the results involving vitamin E as a neuroprotective agent are encouraging, methodology issues, the small size of the studies, the use of multiple chemotherapeutic regimens, lack of blinding, and lack of primary outcome measures make the data less than convincing[6].

Many early reports suggest a possible protective effect of exercise and functional training on CIPN. Therefore, medical exercise to improve muscular strength and sensorimotor functions can be offered to patients at risk of developing CIPN.

CONCLUSION

This article contributes to draw attention to this important and limiting condition, either on the patients' treatment or on the patients' quality of life. It also contributes to gather evidence on preventive measures that reduce the incidence of CIPN.

AUTHORS' CONTRIBUTIONS

Pedro Miguel Parreira da Silva
Statistical analysis, Data Collection, Conceptualization, Resource Management, Project Management, Research, Methodology, Writing - Preparation of the original
Vanessa Capelo Feijão
Statistical analysis, Data collection, Conceptualization, Resource Management, Project Management, Research, Methodology, Writing - Preparation of the original
Maria Teresa Gonzalez Fontinhas
Writing - Review and Editing, Supervision, Validation

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