

Chemotherapy induced neuropathy in clinical practice

Neuropatía inducida por quimioterapia en la práctica clínica

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RESUMEN

El dolor neuropático es un síntoma común en los pacientes con neuropatía periférica causada por agentes quimioterápicos. Los síntomas son indistinguibles de los causados por otras neuropatías tóxicas, es de predominio sensitivo y presenta una distribución en guante o media asociada a un dolor quemante. La neuropatía autonómica es causa frecuente de constipación.

Existen algunos factores de riesgo para la neuropatía asociada a quimioterapia. Los pacientes con neuropatía hereditaria asintomática, pueden tornarse sintomáticos después de la quimioterapia; otras enfermedades como la diabetes aumentan el riesgo de neuropatía. Dentro de una familia de agentes quimioterápicos, unos causan mas neuropatía que otros, por ejemplo en el grupo de las drogas que contienen platino, CDDP y oxaplatino son los más neurotóxicos. Cuando la dosis total de CDDP es superior a 300mg/m² la incidencia de neuropatía se duplica. El uso simultáneo de dos o más medicamentos aumenta el riesgo y la severidad de los síntomas neuropáticos.

El manejo de la neuropatía inducida por quimioterapia incluye diversas estrategias como la disminución de la dosis y el uso de neuroprotectores como glutamina y vitamina E. El manejo del dolor se hace con medicamentos y terapias física y ocupacional.

PALABRAS CLAVE: dolor neuropático, neuropatía periférica, diabetes, oxaplatino, CDDP, quimioterapia, causalgia.
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SUMMARY

Neuropathic pain is a common symptom amongst patients with chemotherapy induced peripheral nerve neurotoxicity, and symptoms are indistinguishable from those seen with toxic neuropathy from other causes. The neuropathy is predominantly sensory and follows a glove-stocking distribution and associates with burning pain. Autonomic neuropathy manifested as constipation frequently occurs. There are some risk factors for neuropathy caused by chemotherapy: patients with asymptomatic hereditary neuropathies can become symptomatic after the administration of chemotherapy, others comorbidities like diabetes are also important. Within a drug family there are some agents that are more likely to cause neuropathy than others; among platinum agents, CDDP and oxaliplatin are the most neurotoxic; in the case of CDDP associated neuropathy, the incidence doubles when the cumulative dose exceeds 300 mg/m². The simultaneous administration of two or more neurotoxic agents increases the risk and severity of neuropathy related symptoms.

Management of chemotherapy induced neuropathy included diverse strategies such: dose reduction and neuroprotection with different agents, like E vitamin and glutamine. Pain management takes place with usual drugs and physical and occupational therapy.

KEY WORDS: complex regional pain syndromes, peripheral nervous system diseases, cisplatin, chemotherapy.
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INTRODUCTION

In the past bone marrow suppression was the most frequent dose limiting toxicity in patients receiving chemotherapy for cancer. Nowadays with the availability of growth factors, higher doses of these agents can be given making the involvement of the peripheral nervous system a frequent limiting toxicity. Furthermore some of the new chemotherapy agents, like oxaliplatin, have a predilection for the peripheral nervous system side effects. This review will describe the characteristics of the most frequent chemotherapy induced neuropathies, strategies to try to prevent this complication, and finally will give treatment recommendations for the neuropathy and symptom relief once it has developed.

EPIDEMIOLOGY

The incidence of this complication varies according to predictive risk factors as described below. Although the frequency of this complication in the general oncologic population is unknown it is considered rare. In a survey that we did of 33 patients in the infusion room 21 per cent reported symptoms that were attributed to chemotherapy induced neuropathy. Even more severe neuropathic pain was a common symptom amongst patients with chemotherapy induced peripheral nerve neurotoxicity. One of the difficulties is that patients usually do not report the neuropathic symptoms, probably because there are expected side effects of the chemotherapy and treatment might be palliative and there might be other causes of pain.

A survey of 30 survivors of testicular or ovarian cancer who received treatment with high doses of cisplatin (CDDP) revealed that more than half had significant neuropathy symptoms that in many cases interfered with work and activities of daily living (1). Therefore neuropathy can be disabling in cancer survivors.

PREDICTIVE RISK FACTORS

The appearance of neuropathy associated to chemotherapy will depend on a variety of factors that could be classified as having to do with the individual patient characteristics, the drug used (Table 1), the cumulative dose and the combination with other drugs.

TABLE 1. MOST FREQUENT CHEMOTHERAPY DRUGS CAUSING NEUROPATHY.

Family	Drugs
Vinca alkaloids	Vincristine Vinblastine Vindesine Vinorelbine
Platinum agents	Cisplatin Carboplatin Oxaliplatin
Taxanes	Paclitaxel Docetaxel

Patient characteristics: patients with asymptomatic hereditary neuropathies can become symptomatic after the administration of chemotherapy (2). Genetic polymorphisms of glutathione-s-transferases, which may act as detoxifying enzymes for chemotherapy agents, are associated with a higher incidence of oxaliplatin related neuropathy (3). In addition other comorbidities like diabetes mellitus and alcohol abuse increase the risk of this complication when potentially neurotoxic chemotherapy is used.

Chemotherapy agent: within a drug family there are some agents that are more likely to cause neuropathy than others. For example, in the taxane family, paclitaxel is more likely to be associated with neuropathy than its semisynthetic analogue, docetaxel.

Chemotherapy dose: for most drugs the incidence and severity of the neurotoxicity will vary according to the cumulative dose. In the case of CDDP associated neuropathy, the incidence doubles when the cumulative dose exceeds 300 mg/m²(2).

Chemotherapy combinations: the simultaneous administration of two or more neurotoxic agents increases the risk and severity of neuropathy related symptoms. In addition patients previously exposed to a neurotoxic agent will be more likely to develop neuropathy when administered with another potentially neurotoxic chemotherapy.

CLINICAL CHARACTERISTICS

The symptoms of neuropathy caused by

chemotherapy are indistinguishable from those seen with toxic neuropathy from other causes. With platinum derivatives and taxanes the clinical manifestations usually persist and increase, or can appear, after stopping the chemotherapy. Sensory manifestations are the initial and predominant symptom, while weakness is usually delayed and subtle. Sensory loss initially localizes in the distal lower limbs and advances proximally, associated with upper extremity involvement in a similar progressive distribution resulting in the distal stocking-and-glove pattern. Autonomic dysfunction may be seen, especially with vincristine. Gait might be severely impaired because of sensory ataxia. Painful paresthesias and allodynia might be the most disturbing symptoms for the patient.

Vinca alkaloids: Vincristine is the most neurotoxic drug of this family, being neuropathy its dose limiting toxicity. It causes a mixed sensory-motor axonal neuropathy with early loss of reflexes, non-painful paresthesias and foot drop. Autonomic neuropathy manifested as constipation frequently occurs. The neuropathy is usually reversible within weeks to months after stopping the drug, although on occasions there is permanent disability.

Platinum agents: CDDP and oxaliplatin are the most neurotoxic agents of this chemotherapy class. The appearance of chronic neuropathy correlates with the cumulative dose, and it is usually sensory with a minor motor component, and can progress to severe disability from sensory ataxia. In addition, oxaliplatin can cause, during the infusion or within hours of completion, acute neurologic symptoms characterized by cold induced paresthesias, laryngospasm and muscle contractions.

Taxanes: paclitaxel is the taxane most frequently causing neuropathy. The neuropathy is predominantly sensory, follows a glove-stocking distribution and associates with burning pain. There might be loss of deep perception with sensory ataxia. Motor involvement is unusual and when present affects the distal toe extensors.

MANAGEMENT OF CHEMOTHERAPY INDUCED NEUROPATHY

Identify individuals at high risk: patients

who are identified at high risk of developing neuropathy and who require of neurotoxic chemotherapy for treatment of cancer should be followed very closely. If symptoms appear even if they are mild consider decreasing or stopping the agent, since symptoms might progress to severe disability. In patients with ovarian cancer, dose reduction in patients who develop mild neuropathy symptoms seems to decrease the incidence of severe neuropathy (4). Whenever possible avoid the concomitant use of other medications that might have peripheral nervous system toxicity.

Neuroprotection: different interventions have been proposed for the prevention of chemotherapy induced neuropathy. Calcium and magnesium infusions have been used for protection from oxaliplatin neurotoxicity (5). In a small controlled study, vitamin E decreased the risk of neuropathy associated to CDDP, paclitaxel or their combination (6). A recent controlled trial demonstrated that glutamine decreases the incidence of neuropathic symptoms after oxaliplatin based chemotherapy (7).

Neuropathic pain treatment: the analgesics and treatment algorithm for the treatment of neuropathic pain secondary to chemotherapy are guided by that same principles used for nerve injury pain from other causes (8). Physical and occupational therapy help in the management of pain, decreasing disability and improving quality of life.

REFERENCES

1. Ostchega Y, Donohue M, Fox N. High-dose cisplatin-related peripheral neuropathy. *Cancer Nurs* 1988;11:23-32.
2. Stillman M, Cata JP. Management of chemotherapy-induced peripheral neuropathy. *Curr Pain Headache Rep* 2006;10:279-87.
3. Lecomte T, Landi B, Beaune P, Laurent-Puig P, Llorca MA. Glutathione S-transferase P1 polymorphism (Ile105Val) predicts cumulative neuropathy in patients receiving oxaliplatin-based chemotherapy. *Clin Cancer Res* 2006;12:3050-6.
4. Markman M. Can we do a better job preventing clinically-relevant peripheral neuropathy resulting from carboplatin/paclitaxel chemotherapy? *Cancer Invest* 2004;22:471-3.
5. Siau C, Bennett GJ. Dysregulation of cellular calcium homeostasis in chemotherapy-evoked painful peripheral neuropathy. *Anesth Analg* 2006;102:1485-90.
6. Argyriou AA, Chroni E, Koutras A, Ellul J, Papapetropoulos S, Katsoulas G, et al. Vitamin E for

prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. *Neurology* 2005;64:26-31.

7. Wang WS, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, et al. Oral glutamine is effective for preventing oxaliplatin-induced neuropathy in colorectal cancer patients. *Oncologist* 2007;12:312-9.

8. Smith EL, Whedon MB, Bookbinder M. Quality improvement of painful peripheral neuropathy. *Semin Oncol Nurs* 2002;18:36-43.