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Review

Basic science and clinical management of painful and non-painful chemotherapy-related neuropathy

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HIGHLIGHTS

- Peripheral neuropathy is a common neurologic side effect of chemotherapy treatment
- Functional and anatomical changes occur at the level of peripheral and central nervous system
- Diagnosis is generally made at the bedside after through history and physical

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting toxicity of several chemotherapeutics used in the treatment of all the most common malignancies. There are several defined mechanisms of nerve damage that take place along different areas of the peripheral and the central nervous system. Treatment is based on symptom management and there are several classes of medications found to be efficacious in the treatment of neuropathic pain. Neuropathic pain that persists despite appropriate pharmacotherapy may respond to interventional procedures that span a range of invasiveness. The purpose of this review article is to examine the basic science of neuropathy and currently available treatment options in the context of chemotherapy induced peripheral neuropathy.

Contents

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Introduction

Chemotherapy-induced peripheral neuropathy is the most common neurologic complication of cancer treatment, particularly with the use of platinum-derived agents, taxanes, vinca alkaloids and proteasome inhibitors which are first-line agents in the treatment of solid tumors [1]. Chemotherapy regimens that utilize combination therapy may potentiate the sequela of neuropathy through agents that produce nerve damage via different mechanisms of action. Initial presentation begins with decreased vibration sense in the toes and loss of the ankle jerk reflex. Further, neuropathy may present as sensory deficits, loss of motor function and pain due to damage that occurs at multiple locations along the peripheral and central nervous system. It is estimated that up to 90% of all cancer patients treated with chemotherapy will be affected by chemotherapy-induced peripheral neuropathy [2]. By example, the development of neuropathy is the most common reason for altering a platinum-based chemotherapy regimen, either by decreasing dose and frequency or by selecting a different therapeutic agent [3]. Depending on the chemotherapy regimen, chemotherapy-induced painful peripheral neuropathy may self-resolve in weeks or persist for years (see Table 1.) [4–6].

Studies on the pathophysiology of chemotherapy induced peripheral neuropathy suggest anatomical and/or functional changes of intraepidermal nerve fibers, primary sensory neurons, CNS neurons, and involvement of glial and immune cells. Currently there is no method of preventing chemotherapy-induced peripheral neuropathy. Treatment is focused mainly on the management of the clinical symptom of neuropathic pain. Our aim is to review what is known about the basic science of neuropathy and also about the currently available treatment options. In doing so, we will focus on chemotherapy induced peripheral neuropathy.

Etiology and pathology of neuropathy

The incidence of peripheral neuropathy during and after the treatment of malignancies is not well-defined, although peripheral neuropathy is known to be a primary dose-limiting toxicity. Among women with ovarian cancer, up to 51% may experience peripheral neuropathy after chemotherapy manifesting especially as numbness and tingling in the hands and feet [7]. In the study of the addition of paclitaxel to cisplatin and doxorubicin for the treatment of advanced endometrial cancer, out of a total of 1203 patients 46.5% reported some form of peripheral neuropathy and 13.2% reported a CTCAE grade 2 neuropathy, with moderate symptoms limiting instrumental activities of daily living [8].

Given the widespread use of common neurotoxic chemotherapeutic agents in the treatment of different malignancies, there is a high risk of peripheral neuropathy developing as an adverse effect. Ovarian cancer is treated with a platinum-based agent such as carboplatin and may be combined with a taxane. High risk gestational trophoblastic neoplasia may require combination therapy including vincristine or cisplatin. Cisplatin and paclitaxel are also used in the treatment of cervical cancer [9]. While bevacizumab alone has not been shown to cause sensory neuropathy, product information supplied by the manufacturer notes a possible increase in the rate of sensory neuropathy when used in combination with paclitaxel. In addition to systemic therapy, radiation therapy and surgery may be indicated for the treatment of gynecologic malignancies.

Nerve injury can occur via several mechanisms during the course of treatment for cancer, and bears consideration in patients who undergo multimodal therapy. Solid tumors may cause local nerve compression depending on size and location. Worsening neuropathy in the territory of a tumor may indicate progression of disease. Surgical resection and lymph node dissection can cause immediate nerve injury due to the placement of surgical tools for retraction and stretching of tissues or delayed injury through the development of postsurgical adhesions. This may present as a non-specific visceral pain. Radiation therapy in high doses causes damage to surrounding structures which may include tumor adjacent nerves and plexuses, such as the lumbosacral plexus during irradiation of pelvic organs.

Pathophysiology

Due to the important role peripheral neuropathy plays in determining the course of cancer treatment, significant research has gone into

Table 1
Commonly used CIPN-inducing chemotherapy agents [19].

Classification	Agent	Type of nerve damage
Platinum-based compounds	Cisplatin Carboplatin Oxaliplatin	Sensory
Vinca alkaloids	Vincristine Vindesine Vinblastine Vinorelbine	Sensory and motor
Taxanes	Paclitaxel Docetaxel	Sensory and motor
Proteasome inhibitors	Bortezomib	Sensory

Table 2
Commonly used medications for the treatment of chemotherapy-induced neuropathic pain.

Classification	Medication	Starting dosage
Anticonvulsants	Gabapentin[a]	100–300 mg at bed time
	Pregabalin[a]	25–75 mg at bed time
	Carbamazepine	100 mg every 12 h
	Lamotrigine	50 mg/day
Antidepressants	Amitriptyline[a]	10–25 mg/day
	Nortriptyline[a]	10–25 mg/day
	Duloxetine[a]	30–60 mg/day
Topicals	Lidocaine 5% patch[a]	1 patch 12 h on 12 h off
	Lidocaine cream[a]	Apply every 8 h
Opioids	Hydrocodone/acetaminophen	5/325 mg every 4 h as needed
	Morphine	15 mg every 4 h as needed
	Oxycodone	5 mg every 4 h as needed
	Methadone	2.5 mg every 12 h
	Fentanyl patch	12.5 μg/h every 72 h
Other	Tramadol	50 mg once to twice a day as needed for pain

[a] Recommended first-line treatment.