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Review

Chemotherapy-induced peripheral neuropathy: Current status and progress

Jamie R. Brewer [a], Gladys Morrison [b], M. Eileen Dolan [b], Gini F. Fleming [b,*]

[a] Section of Hematology-Oncology, Department of Medicine, University of Chicago Medical Center, 5841 S. Maryland Ave, Chicago, IL 60637, United States
[b] Section of Hematology-Oncology, Department of Medicine, The University of Chicago, Knapp Center for Biomedical Discovery, 900 East 57th Street, Chicago, IL 60637, United States

HIGHLIGHTS

- CIPN is a common toxicity of multiple chemotherapy agents.
- To date there are no reliable genomic biomarkers to predict CIPN.
- New stem-cell derived neuron models are promising to advance the field.

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ABSTRACT

As there are increasing numbers of cancer survivors, more attention is being paid to the long term unwanted effects patients may experience as a result of their treatment and the impact these side effects can have on their quality of life. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common long-term toxicities from chemotherapy. In this review we will briefly review the clinical presentation, evaluation and management of chemotherapy-induced peripheral neuropathy, with a focus on CIPN related to platinum and taxane agents. We will then discuss current clinical models of peripheral neuropathy and ongoing research to better understand CIPN and develop potential treatment options.

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* Corresponding author at: University of Chicago, Section Hematology-Oncology, KCBD 900E 57th St, Chicago, IL 60637, United States.
E-mail address: gfleming@medicine.bsd.uchicago.edu (G.F. Fleming).

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1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is damage to the peripheral nerves caused by exposure to a neurotoxic chemotherapeutic agent. It is a common serious non-hematologic adverse effect of chemotherapy. The precise incidence and prevalence of CIPN vary among agents, combinations, and studies, and many authors note significant under-reporting [1]. The Gynecologic Oncology Group (GOG) reported that with a regimen of eight cycles of carboplatin area under the curve (AUC) 6 and every three week paclitaxel at 175 mg/m^2 in the front-line therapy of ovarian cancer, 36% of patients 70 years and older and 20% of patients under the age of 70 experienced neuropathy of grade 2 or higher [2]. CIPN interferes with optimal treatment of active disease resulting in the need for dose reductions, treatment delays and even premature cessation of chemotherapy, and can lead to long-term debilitating effects that can cause increased morbidity and decreased quality of life. In a study of paclitaxel efficacy and toxicity in older women, there was an increased incidence of paclitaxel related toxic effects that increased with age. In addition, the neurosensory and neuromotor toxic effects seen in older adults were significant and concerning for potential future functional consequences, such as loss of mobility, increased falls and other disability [3].

Chemotherapy-induced peripheral neuropathy most commonly presents as a pure sensory neuropathy with symmetric symptoms typically including numbness, loss of proprioception sense, tingling, pins and needles sensation, hyperalgesia or allodynia in the hands or feet in a stocking-glove distribution [4]. Occasionally there can be damage to motor fibers resulting in a motor neuropathy, which occurs more commonly with paclitaxel and vincristine. Autonomic neuropathy is seen most commonly with vinca alkaloids and can be associated with orthostatic hypotension, severe constipation and erectile dysfunction [5]. A review of systems should be completed prior to the initiation of potentially neurotoxic chemotherapy to establish a baseline assessment of patient functionality and symptoms.

CIPN is typically dose-dependent [6]. It can occur at any point after the initiation of treatment including weeks to months after treatment has ended. Late presentations are particularly common with cisplatin. CIPN is commonly associated with exposure to platinum agents (cisplatin, carboplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (particularly vincristine), epothilones (such as ixabepilone) thalidomide and bortezomib [4]. Although upfront identification of patients who will experience CIPN is difficult, risk factors include prior therapy with a neurotoxic agent, diabetes mellitus, folate/vitamin B12 deficiencies, African race, and older age [7,8]. Patients with increased risk should be particularly carefully informed about the risks and symptoms of CIPN and monitored closely during therapy with neurotoxic agents. In some instances, it may be best to consider an alternative regimen (e.g. substitution of docetaxel or liposomal doxorubicin for paclitaxel in therapy of ovarian cancer). In addition to metabolic or medical conditions that may increase risk for CIPN, numerous genetic variants have been identified that are associated with an increased risk of developing CIPN. However, to date none of these genetic variants have been replicated in independent studies [8–10].

Unfortunately, to date there are no agents that have been successful in the prevention of chemotherapy-induced peripheral neuropathy [11]. There has also been limited progress in discovery of agents that show benefit in the treatment of CIPN. None of the available therapies reverse the neuropathy although some may ameliorate the pain. Many agents are used based on data from management of other forms of neuropathy, e.g. diabetic neuropathy [12]. However Smith et al., [12] demonstrated a benefit for duloxetine over placebo specifically in the treatment of chemotherapy-induced peripheral neuropathy.

2. Clinical features of CIPN associated with taxanes and platinum agents

2.1. Taxanes

Paclitaxel and docetaxel typically cause a sensory neuropathy described as paresthesia, numbness or neuropathic pain in the hands and/or feet. Deficits in motor function are less common, but can present in severe cases. The risk of taxane-induced peripheral neuropathy increases with cumulative dose received [6]. Some studies have reported less neurotoxicity with weekly paclitaxel dosing in comparison to 3-week dosing when the total dose is kept similar [13]. For example, in the MITO-7 study, a randomized phase 3 trial of carboplatin plus paclitaxel once a week at 60 mg/m^2 versus paclitaxel every three weeks at 175 mg/m^2 in patients with advanced ovarian cancer, 17% of patients experienced grade 2 or higher neuropathy in the every 3 week arm versus only 6% in the weekly arm. However most commonly used weekly paclitaxel regimens involve a higher cumulative dose of paclitaxel and neuropathy rates with such weekly regimens are not lower. The Japanese Gynecologic Oncology Group (JGOG) administered paclitaxel at a dose of either 80 mg/m^2 weekly or 180 mg/m^2 every three weeks (along with carboplatin AUC 6), and reported 7% grade 3 or higher sensory and 5% grade 3 or higher motor neuropathy in the weekly group versus 6% grade 3 or higher sensory and 4% grade 3 or higher motor neuropathy in the every three week group [14]. In a trial randomizing metastatic breast cancer patients to single agent paclitaxel 175 mg/m^2 every three weeks versus paclitaxel 80 mg/m^2,weekly, the patients on the weekly arm were initially given the first six infusions at 100 mg/m^2; this resulted in a 30% incidence of grade 3 peripheral neuropathy, and the trial was subsequently amended to start weekly infusions at 80 mg/m^2 [15].

Most patients can expect symptom improvement or resolution within a 3–6 month period after the discontinuation of treatment, but more severe cases tend to be less likely to resolve [16]. Pignata et al. reported on 120 ovarian cancer patients who received six cycles of front-line chemotherapy with carboplatin AUC 5 and paclitaxel 175 mg/m^2 every three weeks. There was a 15% probability of still having neuropathy (mostly grade 1) 6 months after completion of chemotherapy, and an 11% chance of still experiencing neuropathy at 2 years after completion of chemotherapy [17]. In one case–control study of breast cancer patients treated with weekly paclitaxel, diabetes mellitus (DM) was the only independent factor found to predict for delayed recovery. After 2 years, 68.7% of patients with DM (vs 29.2% of women without DM) still experienced CIPN, which was functionally significant (grade 2–3) in 18.2% [18].

Administration of paclitaxel can be associated with an acute pain syndrome characterized by development of myalgia and arthralgia within 1–4 days of paclitaxel infusion [19]. This is more common with higher single doses (i.e. more common with an every three week regimen than with a weekly regimen). Severe acute pain syndrome with paclitaxel has been reported to be predictive of development of chemotherapy-induced sensory neuropathy [19].

Docetaxel is generally less neurotoxic than paclitaxel at standard dosage. The Scottish Gynaecological Cancer Trials Group front line ovarian cancer trial reported a rate of 11% grade 2 or higher neurosensory