Pain in Platin-Induced Neuropathies: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Platin-induced peripheral neuropathy (PIPN) is a common cause of PN in cancer patients. The aim of this paper is to systematically review the current literature regarding PIPN, with a particular focus on epidemiological and clinical characteristics of painful PIPN, and to discuss relevant management strategies.

Methods: A systematic computer-based literature search was conducted on the PubMed database.

Results: This search strategy resulted in the identification of 353 articles. After the eligibility assessment, 282 articles were excluded. An additional 24 papers were identified by scanning the reference lists. In total, 95 papers met the inclusion criteria and were used for this review. The prevalence of neuropathic symptoms due to acute toxicity of oxaliplatin was estimated at 84.6%, whereas PN established after chemotherapy with platin was estimated at 74.9%. Specifically regarding pain, the reported prevalence of pain due to acute toxicity of oxaliplatin was estimated at 55.6%, whereas the reported prevalence of chronic peripheral neuropathic pain in PIPN was estimated at 49.2%.

Conclusion: Peripheral neuropathy is a common complication in patients receiving platin and can be particularly painful. There is significant heterogeneity among studies regarding the method for diagnosing peripheral neuropathy. Nerve conduction studies are the gold standard and should be performed in patients receiving platin and complaining of neuropathic symptoms post-treatment.

Keywords: Cancer; Chemotherapy; Pain; Platin; Polyneuropathy

INTRODUCTION

The term “peripheral neuropathy” (PN) refers to various disorders of the peripheral nervous system, including single and multiple (asymmetric) mononeuropathies, symmetrical involvement of many nerves (polyneuropathy), or the sole involvement of the dorsal root ganglia [1, 2].

PN is very prevalent in cancer patients [3] and can be a direct or an indirect complication...
of cancer or cancer-related treatment, a pre-existing comorbidity not related to cancer, or part of a paraneoplastic syndrome [4–7].

The vast majority of chemotherapy-induced PN (CIPN) is caused by neurotoxic chemotherapy schemes, with platins (cisplatin, oxaliplatin, carboplatin) constituting the leading source of treatment-induced PN in cancer. Contrary to the perception that painful neuropathies are largely caused by diabetes, other forms of PN can be particularly painful, leading to poor quality of life [2]. Therefore, platin-induced peripheral neuropathy (PIPN) should be considered a major cause of pain in cancer patients [8].

The aim of this paper is to systematically review the epidemiological and clinical characteristics of painful PIPN and provide an overview of relevant management strategies.

METHODS

Literature Search Strategy

A systematic computer-based literature search was conducted August 15, 2017, on the PubMed database. For the search, we used three Medical Subject Headings (MeSH) terms in either the title or abstract, as follows: (1) “neuropathy” or “ganglionopathy” or “neuropathy” or “polyneuropathy”; (2) “pain” or “painful”; (3) “chemotherapy” or “platin” or “platins” or “oxaliplatin” or “cisplatin”. Articles were limited to English language, species to human, and with full text available. We also perused the reference lists of the papers in order to identify papers not found through the search strategy.

Inclusion and Exclusion Criteria

Articles eligible for inclusion in the review were required to meet the following criteria:
1. Involved case series with platin-induced PN.
2. Studied human adult subjects.

The following were excluded:
1. Book chapters, reviews, letters to the editor, and editorials that did not provide new data.
2. Papers providing incomplete clinical or neurophysiological data about the single cases/case series.

Data Extraction

Data were extracted from each study in a structured coding scheme using Microsoft Excel, and included information on the article identification, year of publication, evaluation period, total number of subjects, gender, age, presence of pain in general, presence of pain secondary to the neuropathy, neurophysiological type of neuropathy, course of symptoms, type of cancer, and type of platin. We also collected information about the time point of diagnosis in each study, and whether they referred to acute toxicity or cumulative effect after completion of all cycles of chemotherapy. Papers referring to symptoms during chemotherapy without specifying the time point (such as which cycle) were not considered for analysis.

Statistical Analyses

A database was developed using IBM SPSS Statistics software (version 23.0 for Mac; IBM Corp., Armonk, NY, USA). Frequencies and descriptive statistics were examined for each variable. The primary outcome of interest was the proportion of patients who experienced pain because of PIPN.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Search Results

This search strategy resulted in the identification of 353 articles. A total of 282 articles were excluded during the eligibility assessment, and
25 additional papers were identified by scanning the reference lists. Therefore, 96 papers met the inclusion criteria and were used for this review [9–104]. These studies were published between 1980 and 2017. Figure 1 illustrates the study selection process.

Full clinical and neurophysiological data were further extracted from 54 papers [29–82] involving a total of 8159 patients (49.8% male) who received chemotherapy that included platins. The age of the patients ranged from 18 to 85 years (mean 65.9 years). The demographic and clinical characteristics of these patients are summarized in Table 1.

Forty-six papers provided data for the prevalence of PN in patients who received platins in their chemotherapeutic scheme. Of these, 22 papers reported PN during chemotherapy, 14 reported PN after completion of chemotherapy, and three specifically reported the acute toxic effects of oxaliplatin. Seven papers did not clearly specify the time point where PN occurred. The prevalence of established PN after chemotherapy was estimated at 56.5%.

In 16 studies, patients received only platins, not combined with another neurotoxic chemotherapeutic agent. Of these, four papers...
reported PN during chemotherapy, eight reported PN after completion of chemotherapy, and three specifically reported the acute toxic effects of oxaliplatin. One paper did not clearly specify the time point at which PN occurred. The prevalence of neuropathic symptoms due to acute toxicity of oxaliplatin was estimated at 84.6%, whereas established PN after chemotherapy with platin was estimated at 74.9%. Of note, in only two studies—which provided data about the prevalence of PIPN—was PN confirmed with a full neurophysiological assessment. Specifically regarding pain, the reported prevalence of pain due to acute toxicity of oxaliplatin was estimated at 55.6%, whereas the reported prevalence of chronic peripheral neuropathic pain in PIPN was estimated at 49.2%.

Epidemiological Characteristics of PIPN

A meta-analysis of 31 studies providing data from 4179 patients established that the prevalence of CIPN was 68.1% (95% CI 57.7–78.4%) when measured in the first month after chemotherapy completion, 60.0% (95% CI 36.4–81.6%) at 3 months, and 30.0% (95% CI 6.4–53.5%) at 6 months or more [9]. However, these figures refer to a variety of chemotherapeutic agents. Moreover, the diagnosis of the neuropathy was not made via nerve conduction studies (NCS) in all cases; in some studies, neuropathy was based only on quantitative sensory testing (QST), neurological examination, and/or questionnaires [9]. Among only those studies in which NCS or QST was used for assessment of neuropathy, the prevalence of CIPN was higher: 73.3% (95% CI 58.6–87.3) within 1 month of chemotherapy cessation, 70.1% (95% CI 41.8–98.4) at 3 months, and 39.9% (95% CI 3.9–76.0) at 6 months or greater. A limitation of these figures, however, is that abnormal results obtained by QST without having performed NCS does not definitively establish the presence of PN, and thus the above-mentioned percentages reflect the presence of neuropathic symptoms rather than CIPN.

Specifically concerning platinis, the incidence of neuropathic symptoms for cisplatin ranged from 49% to 100%, whereas carboplatin was reported to be less neurotoxic, with neuropathic symptoms observed in 13% to 42% of cases [10, 11]. The presence of acute oxaliplatin-induced neuropathic symptoms has been reported in 85–95% of patients, and these symptoms have been observed in a chronic persistent form in approximately 16–21% of patients [11, 12, 56].

Risk Factors for PIPN

Several risk factors have been associated with the development of painful PIPN. Wang et al. [32] reported that female sex, patient’s level of functioning (assessed by the Eastern Cooperative Oncology Group performance status scale), body mass index (BMI), and baseline opioid use were associated with increased severity of oxaliplatin-induced peripheral neuropathy [32]. Attal et al. [58] revealed a significant relationship between the severity of acute signs and symptoms of oxaliplatin neurotoxicity after three cycles of chemotherapy and the occurrence and severity of chronic residual neuropathic symptoms as assessed by QST and the Neuropathic Pain Symptom Inventory (NPSI) after 1 year.

Table 1 Description of studies included in the review

| Parameter                        | Value |
|----------------------------------|-------|
| Number of papers*                | 54    |
| Total number of patients         | 8159  |
| Number of patients per study, mean (SD) | 151.1 (419.6) |
| Male: Female                     | 1:1   |
| Mean age, in years               | 65.9  |
| Diagnosis of PN                  |       |
| Questionnaires only (%)           | 12 (22.2) |
| Nerve conduction studies (%)      | 3 (5.6) |
| Quantitative sensory testing (%)  | 7 (13.0) |
| Clinical examination (%)          | 8 (14.8) |
| Not reported (%)                  | 24 (44.4) |
| Platin-induced PN (%)             | 73.3  |
| Painful PIPN (%)                  | 45.8  |

*Providing full clinical and neurophysiological data. SD standard deviation, PN peripheral neuropathy.
Moreover, the duration of neuropathic symptoms was observed to increase as the cumulative dose of platin increased [69]. For example, Leonard et al. found that after the first cycle of chemotherapy, the median duration of dysesthesia was only 5 days, whereas it was 21 days in patients who received 12 cycles of chemotherapy. The median duration of paresthesia after cycle 1 was 7 days, but after cycle 12 was 21 days or longer [69]. Similarly, in many clinical trials sensory symptoms causing functional impairment have been found in only about 15% of patients after a cumulative dose of 780–850 mg/m² but in 50% of patients at a cumulative dose of 1170 mg/m² [13, 14].

Specifically concerning carboplatin, Take-moto et al. [88] observed a greater visual analogue scale (VAS) score when it was combined with paclitaxel than with docetaxel; additionally, as the number of chemotherapy cycles increased, the carboplatin–paclitaxel-induced neuropathic symptoms became more severe.

Concerning cisplatin, Bezjak et al. [95] demonstrated that in lung cancer survivors, sensory cisplatin-induced neuropathic symptoms were a late effect of cisplatin, persisting for at least 9 months after chemotherapy and affecting quality of life. Similar symptoms have been reported as a late effect of cisplatin in long-term survivors of testicular cancer, and the cumulative dose of cisplatin has been reported to be a major risk factor for the development of toxicity [28].

Not all studies reported screening for pre-existing neuropathy prior to chemotherapy with platins. Also, not all studies reported having excluded patients with other common risk factors for PN such as diabetes, excessive alcohol intake, gluten sensitivity [105, 106], or hereditary neuropathies. Therefore, such comorbidities may have contributed to the development of PN.

Predictors of PIPN

Cold allodynia and hyperalgesia of the hands after three cycles of oxaliplatin treatment was found to be predictive of severe chronic neuropathy [58]. Among a range of cold stimuli, pain induced by a 20 °C stimulus to the hand had the highest predictive value with regard to development of severe chronic neuropathy. The severity of chronic neuropathy was also found to correlate with the duration of cold-evoked symptoms, the intensity of acute neuropathic symptoms, and the intensity of cold-evoked pain [58].

Management

Management of platin induced peripheral neuropathic pain includes pharmacological and non-pharmacological approaches [8].

Antidepressants

Venlafaxine, a serotonin and norepinephrine reuptake inhibitor, was effective in the management of acute neuropathic symptoms in a small series of patients receiving oxaliplatin [100]. Venlafaxine also showed promising preliminary evidence of clinical effectiveness of this combination against chronic neuropathic symptoms in oxaliplatin-induced PN [97]. According to the EFFOX study, complete relief of neuropathic symptoms induced by oxaliplatin was achieved in 31.3% of patients, which is a significantly higher percentage than the 5.3% achieved with placebo [91].

Duloxetine, another serotonin and norepinephrine reuptake inhibitor, was also found to be effective in oxaliplatin-induced painful neuropathy [55]. In an open-label study, Yang et al. demonstrated that duloxetine could be used effectively in low doses (i.e. 60 mg/day) without impairment of renal or liver function—and importantly, without interfering with chemotherapy [55]. More recently, a large placebo-controlled randomized clinical trial showed that duloxetine was more effective than placebo in reducing the average PIPN pain score after a 5-week treatment period [101]. Overall, duloxetine has the largest volume of evidence supporting its use in the treatment of painful PIPN [107].

Nortriptyline, a tricyclic antidepressant, failed to demonstrate effectiveness for treating paresthesia or pain in cisplatin-induced neuropathic symptoms [98].
Anticonvulsants
Topiramate showed promising preliminary evidence of clinical effectiveness of this combination against chronic neuropathic symptoms in oxaliplatin-induced PN [97].

Carbamazepine, on the other hand, does not appear to be beneficial against acute oxaliplatin-induced painful neurotoxicity [99]. Research findings regarding the effectiveness of gabapentin for treating pain caused by PIPN remain controversial. In a phase III randomized, double-blind, placebo-controlled crossover trial, Rao et al. concluded that gabapentin failed to demonstrate any benefit [102], whereas an open-label study by Tsavaris et al. found that gabapentin monotherapy seemed to be well tolerated and useful for the management of chemotherapy-induced neuropathic pain [103]. However, both studies included patients with PN secondary to other chemotherapeutic agents in addition to platins. To date, no study has explored the efficacy of gabapentin alone in patients with PIPN.

Opioids
Liu et al. [89] reported that tramadol in combination with acetaminophen, administered in patients with colorectal or gastric adenocarcinoma, was effective in relieving oxaliplatin-induced peripheral neuropathic pain [89]. Interestingly, this study proposed that the A118G polymorphism of the mu-opioid receptor gene (OPRM1) was a possible mechanism for the reduced response to the combination of tramadol and acetaminophen [89], suggesting that management should be always be tailored to individual patient characteristics.

Topical Drugs
In an open-label study, Filipczak-Bryniarska et al. demonstrated that the high-dose capsaicin patch was effective in treating pain associated with oxaliplatin-induced neuropathy [104]. However, this finding should be interpreted with caution, given the limitations of the study design and small number of the participants.

Non-Pharmacological Approaches
There is some evidence that acupuncture may be beneficial for the treatment of PIPN. In a small case series, Donald et al. [87] reported that patients with oxaliplatin-induced painful neuropathy improved after acupuncture. Wong et al. [96] similarly described a small series of patients with symptoms of pain due to carbo-platin-induced neuropathy who improved after acupuncture. A prospective pilot study by Hsieh et al. [30] showed that laser acupuncture relieved both cold and mechanical allodynia induced by oxaliplatin in gastrointestinal cancer survivors. To date, however, no large randomized controlled trial has been conducted to confirm the effectiveness of acupuncture in managing pain in PIPN. Therefore, the current evidence is weak.

Cunningham et al. [90] reported a case of almost complete resolution of the tingling, numbness, and pain of cisplatin-induced neuropathy with manual therapy (massage) in a patient with stage III esophageal adenocarcinoma. However, as this was based on a single case, this finding should be interpreted with extreme caution.

Henke et al. [84] reported that strength and endurance training in patients receiving platinum-based chemotherapy for lung cancer was effective in managing pain. The authors thus suggested that lung cancer patients should receive enhanced physical activity intervention during palliative chemotherapy.

Diagnosing and Monitoring PIPN

Large Fiber Neuropathy
The gold standard for diagnosing a large fiber neuropathy is NCS. Although centers have many different means of neurophysiologically determining the presence of PN, sensory conduction studies of sural and radial nerves are recommended for the diagnosis of mild, predominantly sensory axonal neuropathy [108]. This should be complemented with at least one motor study, commonly of the tibial nerve, to confirm motor involvement [109, 110]. In the case of PIPN, however, the neuropathy is sensory, affecting the dorsal root ganglia. In a
sensory ganglionopathy, asymmetrical sensory nerve action potentials (SNAPs) or complete absence of SNAPs should be expected [111, 112].

**Small Fiber Neuropathy**

Patients often complain of disabling symptoms such as a burning sensation in the soles or the fingertips, which is a common manifestation of small fiber neuropathy (SFN). Nerve conduction studies assess only large fibers, and therefore, SFN cannot be excluded if NCS are normal.

The gold standard for a diagnosis of SFN is skin biopsy; however, this is an invasive technique and is thus usually avoided. QST is commonly used for assessment of SFN, but this is subjective. Alternatively, nerve morphology can be rapidly assessed using in vivo corneal confocal microscopy. This technique has been used for the detection of various types of neuropathy, including small fiber neuropathy [15]. Fereidoni et al. [35] showed that corneal confocal microscopy was effective in detecting small fiber neuropathy by a marked reduction in corneal nerve morphological parameters in patients with upper gastrointestinal cancer and oxaliplatin- or cisplatin-induced neuropathy.

**Questionnaires**

Several questionnaires have been used for the detection and assessment of PIPN. Particular interest has been focused on the development and validation of questionnaires regarding quality of life in patients with CIPN.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), designed to assess quality of life for cancer patients, is widely used and consists of 30 items comprising five functional scales (physical, role, emotional, cognitive, and social), global health status, and nine symptom scales and single items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. It is also supplemented with specific modules for the different cancer types [16, 17, 83, 84, 95].

The EORTC QLQ-CIPN20 is a quality-of-life questionnaire developed to elicit patient experience of symptoms and functional limitations related to CIPN. It contains 20 items assessing sensory, motor, and autonomic symptoms [18, 86]. The CIPN20 can assess frequency and severity of painful CIPN in a wide range of oncology patient populations.

The L-BASIC [location-based assessment of sensory symptoms in cancer] instrument uses location-specific ratings of sensory symptoms in the cancer population [94]. It is structured such that patients provide a numeric score and an adjectival description for any sensory symptoms, including both pain and neuropathic sensations, present in each of 10 predefined body areas [94].

The Rasch-built Overall Disability Scale for CIPN (CIPN-R-ODS) is a Rasch-built disease-specific interval measure suitable for detecting disability and levels of activity and participation in patients with stable disease [85].

The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire is the Functional Assessment of Cancer Therapy-General (FACT-G) instrument plus an 11-item subscale (Ntx subscale) [19]. It is a chemotherapy treatment effect-specific measurement tool used to evaluate the severity and impact of CIPN symptoms on functional status and health-related quality of life [19]. Questions on the Ntx subscale include the feeling of generalized weakness, numbness or tingling in the hands or feet, and difficulty with fine motor movements [19, 20].

The Total Neuropathy Score (TNS) was initially designed to evaluate diabetic neuropathy [21] and was later validated in patients with CIPN [22]. The TNS includes objective measures, such as pin prick, vibration threshold, and nerve conduction studies, combined with subjective report of sensory, motor, and autonomic items, and the instrument has been tested in a variety of tumor types [22–24, 93].

The chemotherapy-induced neuropathy-specific Neuropathic Pain Scale (NPS-CIN) is a six-item scale used to assess CIPN and related neuropathic pain severity [25, 92, 93].

The Patient Neurotoxicity Questionnaire, comprising two items, defines the incidence
and severity of sensory and motor disturbances [26].

The Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT) contains 36 items that evaluate the occurrence, severity, distress, and frequency of nine neuropathic symptoms, along with 14 items that evaluate neuropathic interference with activities [27].

CONCLUSION

This systematic review has identified the following key points:

1. PN is a common complication in patients receiving platins in their chemotherapeutic regime.
2. PIPN can be particularly painful. Acute toxicity occurs only with oxaliplatin. However, in a significant proportion of patients receiving platins, the pain persists and becomes chronic.
3. There is significant heterogeneity in the methods used to diagnose PN. In many studies, patients were diagnosed based only on questionnaires or clinical examination. Although the use of questionnaires may be adequate for characterizing and monitoring neuropathic symptoms, the gold standard for accurate diagnosis of an established peripheral neuropathy—from a neurological point of view—is NCS. Ideally, this should be performed as a baseline, before the chemotherapy, and should be repeated at the end or when symptoms occur. QST alone is not sufficient for establishing a diagnosis of PN, as it is not objective, and its role is more as an indicator of small fiber involvement; therefore, QST should be complemented with NCS.
4. Small fiber neuropathy is gaining increasing attention in clinical practice; however, further studies are needed in patients receiving platins, as the neuropathic pain that patients experience during chemotherapy with platins is likely often secondary to small fiber involvement, with no involvement of the large fibers.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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