BJA

British Journal of Anaesthesia, 0 (0): 1–13 (2017)

doi: 10.1093/bja/aex229
Review Article

REVIEW ARTICLE

Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): a narrative review

S. J. L. Flatters[1,*], P. M. Dougherty[2] and L. A. Colvin[3]

[1]Wolfson Centre for Age-Related Diseases, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE1 1UL, UK, [2]Division of Anaesthesia, Critical Care and Pain Medicine, Department of Pain Medicine Research, The University of Texas M.D. Anderson Cancer Centre, Houston, TX, USA and [3]Department of Anaesthesia, Critical Care & Pain Medicine, University of Edinburgh, Western General Hospital, Crewe Rd, Edinburgh EH4 2XU, UK

*Corresponding author. E-mail: sarah.flatters@kcl.ac.uk

Abstract

This review provides an update on the current clinical and preclinical understanding of chemotherapy induced peripheral neuropathy (CIPN). The overview of the clinical syndrome includes a review of its assessment, diagnosis and treatment. CIPN is caused by several widely-used chemotherapeutics including paclitaxel, oxaliplatin, bortezomib. Severe CIPN may require dose reduction, or cessation, of chemotherapy, impacting on patient survival. While CIPN often resolves after chemotherapy, around 30% of patients will have persistent problems, impacting on function and quality of life. Early assessment and diagnosis is important, and we discuss tools developed for this purpose. There are no effective strategies to prevent CIPN, with limited evidence of effective drugs for treating established CIPN. Duloxetine has moderate evidence, with extrapolation from other neuropathic pain states generally being used to direct treatment options for CIPN. The preclinical perspective includes a discussion on the development of clinically-relevant rodent models of CIPN and some of the potentially modifiable mechanisms that have been identified using these models. We focus on the role of mitochondrial dysfunction, oxidative stress, immune cells and changes in ion channels from summary of the latest literature in these areas. Many causal mechanisms of CIPN occur simultaneously and/or can reinforce each other. Thus, combination therapies may well be required for most effective management. More effective treatment of CIPN will require closer links between oncology and pain management clinical teams to ensure CIPN patients are effectively monitored. Furthermore, continued close collaboration between clinical and preclinical research will facilitate the development of novel treatments for CIPN.

Key words: cancer pain; neuralgia; paclitaxel

Neuropathic pain, defined as "*Pain caused by a lesion or disease of the somatosensory nervous system*" is a challenging clinical problem, with around 8% of the population suffering from neuropathic pain. Patients suffering from this type of pain report worse pain and disability than those with non-neuropathic chronic pain.[1–3] Neuropathic pain may have an even greater impact on patients than other chronic pain syndromes, with affected individuals rating their quality of life as "worse than death", on the EQ-5D, a validated quality of life measure.[3] Unfortunately, many modern chemotherapeutic agents can

Editorial decision June 6, 2017; **Accepted:** June 20, 2017

cause both acute and chronic peripheral neuropathy - chemotherapy induced peripheral neuropathy (CIPN).[4] During oncological treatment, the severity of the acute syndrome may require reducing the dose of chemotherapy or even stopping it, with potential impact on tumour control and survival.

Chemotherapy-induced painful neuropathy (CIPN) is a major dose-limiting side-effect of several first-line chemotherapeutic agents.[5–10] CIPN is a challenging and complex pain syndrome that we have no effective preventive and limited treatment options for currently. CIPN can have a major and prolonged impact on quality of life for patients. As oncological treatments have advanced, cancer survival has increased significantly, with many patients either being cured of cancer or living for many yr with cancer. Given the prevalence of the common cancers (e.g. breast, ovarian, colorectal) that these chemotherapeutics counteract, CIPN affects several million patients worldwide each yr. CIPN also places a significant economic burden on patients as a result of work-loss and the healthcare system because of its prevalence.[11] Effective collaboration between preclinical and clinical researchers is needed to translate improved understanding of the underlying mechanisms into development of effective preventive and treatment strategies.[12] This review aims to provide an overview of the clinical syndrome, its assessment, diagnosis and treatment, and how our improved understanding of underlying mechanisms contribute to this. While there are, multiple factors contributing to CIPN, we will focus particularly on areas where research findings from several different laboratories have highlighted potentially promising areas for development. These include the role of mitochondrial dysfunction, oxidative stress, immune cells and changes in ion channels in CIPN rodent models.

CIPN: the clinical syndrome

CIPN usually presents as a typical “glove and stocking” neuropathy. Patients describe a range of predominantly sensory symptoms including numbness, parathesia, ongoing/spontaneous pain, hypersensitivity to mechanical and/or cold stimuli in their hands and feet. In more severe cases, loss of vibration sense and joint position sense contribute to the impact on function. Autonomic and motor dysfunction may also occur. Patients can have significant difficulty in essential daily functions including difficulty in fine finger movement such as buttoning clothing, and unsteady gait (numbness, loss of joint position sense); pain on walking (mechanical hypersensitivity); inability to remove items from a fridge, or exacerbation in cold weather (cold hypersensitivity). CIPN may present acutely, during chemotherapy, such as is commonly seen with platinum based compounds.[13] It may also occur after treatment has finished - a phenomenon known as “coasting” -where either mild neuropathy worsens, or new CIPN develops. This is challenging for oncologists, as there is no indication during chemotherapy to allow dose modification in order to reduce CIPN.[14] Pain and sensory abnormalities can persist for months or yr after the cessation of chemotherapy.[5 15 16] Therefore, patients may well be cancer-free, but suffering a debilitating neuropathy evoked by their cancer treatment.

Peripheral neuropathy has been long associated with established drugs such as platinum agents (e.g. oxaliplatin), vinca alkaloids (e.g. vincristine), and taxanes (e.g. paclitaxel). However, newer, more targeted drugs, such as bortezomib, eribulin and ixabepilone[4,17] are also associated with significant incidence of peripheral neuropathy. All of these chemotherapeutics have different mechanisms by which they evoke their anti-mitotic effects (e.g. perturbation of microtubule dynamics, DNA cross-linking, proteasome inhibition). Whether all these drugs evoke neurotoxicity by similar mechanisms remains to be determined.

Prevalence and risk factors for CIPN

The prevalence of CIPN varies between different agents, with reported rates varying from 19% to more than 85%.[18] While the agent and dose used is an important determining factor, there is no doubt that the lack of a gold standard agreed assessment tool impacts on reported rates of CIPN.[19] A systemic review and meta-analysis of CIPN incidence and prevalence with paclitaxel, bortezomib, cisplatin, oxaliplatin, vincristine or thalidomide (solo or combination) treatment demonstrated the persistence of this disorder.[20] CIPN was observed in 68.1%, 60%, and 30% of patients, within the first month, at three months, and at $\geq$ six months, respectively, after cessation of chemotherapy, when looking at chemotherapy as a whole. While type of chemotherapy is important, at least part of the variability in reported prevalence was as a result of differences in the timing of assessment.[20]

A number of possible risk factors have been identified, including genetic factors, although there is a need for more systematic evaluation of potential contributory factors. A number of single nucleotide polymorphisms potentially associated with CIPN have been identified through Genome Wide Association Studies. Proteins with a range of functions have been identified, including axon outgrowth, sodium channels and neuronal apoptosis.[21–25] Studies of clinical risk factors are limited, often with small sample sizes. From the available data for CIPN, a history of neuropathy before starting chemotherapy (e.g. diabetic), impaired renal function with reduced creatinine clearance, and a history of smoking may all increase risk of developing CIPN. The cumulative dose of chemotherapy is well recognized as a major risk factor, with growing interest in the effect of concentrations of circulating growth factors, or other biological markers as a means of early identification of quantifiable risk factors.[20]

Assessment and diagnosis of CIPN

There is currently no widely accepted, standardized assessment approach for diagnosis of CIPN *per se*. There are a number of guidelines on assessment and diagnosis of neuropathic pain in general, which may be useful in CIPN.[26–28] Onset of symptoms during, or shortly after, chemotherapy is normally described, often affecting feet first, then with impairment of sensation in fingers and hands. If patients describe abnormalities in sensation, or these are detected on clinical examination, then CIPN should be suspected. Early identification allows treatment decisions about continuation, or not, of chemotherapy to be better informed, and allows initiation of anti-neuropathic agents, if appropriate.[29 30]

Accurate understanding of the epidemiology of CIPN, early identification and treatment of the clinical problem and evaluation of new treatments would all be improved by a standardized approach. The aim of the CI-PeriNomS Study Group was to assess reproducibility and validity of existing measures, and if necessary develop a simple and reproducible assessment for CIPN to try and meet this need.[31] A number of the tools available for assessing CIPN have been robustly assessed and show good reliability and validity (see Table 1).[39] From this, abnormalities