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Review

Neurophysiological and clinical outcomes in chemotherapy-induced neuropathy in cancer

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HIGHLIGHTS

- Peripheral neuropathy is a significant source of long term morbidity in many cancer survivors.
- Neurophysiologic techniques provide objective biomarkers for monitoring and understanding pathology.
- Combined with patient reported outcomes, these provide comprehensive assessment in clinical trials.

ABSTRACT

Chemotherapy induced peripheral neuropathy (CIPN) is a significant toxicity of cancer treatment, with the potential to affect long-term function and quality of life in cancer survivors. There remains a lack of consensus around optimal assessment techniques. While current approaches to CIPN assessment are focused on clinical grading scales, it is becoming increasingly evident that a more comprehensive multimodal assessment package is necessary to accurately characterise the impact of CIPN as well as gauge the utility of neuroprotective mechanisms. Neurophysiological techniques provide objective biomarkers and may enable early detection of toxicity while patient reported outcomes are necessary to determine the significance of symptoms to individual patients. In addition to providing an objective assessment, clinical neurophysiological techniques provide important insights into the contributory pathophysiological mechanisms of CIPN with different chemotherapy agents. There is a paucity of implementation of these techniques in the clinical trial setting. The present Review aims to facilitate the use of neurophysiological studies as part of comprehensive assessment packages for the monitoring of CIPN by summarising current understanding of neurophysiological changes that underlie the development of neuropathy, clinical presentations and patient reported outcomes as well as advantages and limitations of current techniques for the neurophysiological assessment of CIPN.

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1. Introduction

Long-term side effects of cancer therapy are of increasing significance in the context of substantial improvement in cancer survivorship. With more than 32.6 million cancer survivors worldwide, the impact of long-term toxicities arising from chemotherapy treatment is substantial (Ferlay et al., 2013). Chemotherapy-induced peripheral neuropathy (CIPN) is a significant toxicity associated with vinca alkaloids, platinum compounds, taxanes, thalidomide derivatives and proteasome inhibitors used to treat many common cancers including breast, ovarian, colorectal and haematological malignancies (Table 1). CIPN impacts on tolerability of treatment, leading to dose reduction and premature cessation, potentially impacting on treatment efficacy. Further, CIPN often produces persistent symptoms, leading to long-term detrimental effects on patient quality of life and function (Ezendam et al., 2014; Eckhoff et al., 2015). It is imperative that objective, evidence-based techniques are established, to monitor short-term outcomes and long-term morbidity of CIPN in cancer survivors.

Whereas early clinical studies identified patients with neuropathy purely based on their clinical presentation, neurophysiological parameters are being incorporated more frequently into CIPN assessment protocols (Openshaw et al., 2004; Cavaletti et al., 2007, Cavaletti et al., 2010). Neurophysiological techniques provide objective evidence of nerve dysfunction and enable detection of physiological changes prior to clinical symptoms, as well as enhancing understanding of the neuropathological mechanisms to inform future prevention strategies. There remains a gap in implementation of neurophysiological measures in CIPN assessment, particularly in the clinical trial setting. The purpose of this Review is to summarise current understanding of the neurophysiological changes that underlie neuropathy due to chemotherapy treatment, identify corresponding clinical presentations and

Table 1
Clinical manifestations of CIPN with different chemotherapy agents.

Chemotherapy agent	Clinical features			Ref	*N
	Sensory	Motor	Autonomic		
Vincristine	Distal paraesthesia, numbness, hypaesthesia Early distal hypo or areflexia	Distal weakness with higher doses	Constipation and postural hypotension	1–5	104
Paclitaxel	Distal paraesthesia, pain, numbness and hypaesthesia Distal hypo or areflexia	Myalgia common, distal weakness uncommon and late in treatment course	Rare	6–12	275
Cisplatin	Distal paraesthesia, dysaesthesia, numbness and reduced vibration sense; occasional Lhermitte's phenomenon Distal hypo or areflexia	Rare	–	13–20	193
Oxaliplatin	*Acute syndrome:* Cold induced perioral or limb paraesthesia, pharyngolaryngeal dysaesthesia, jaw pain	*Acute syndrome:* Jaw and muscle cramps	–	21–25	242
	Chronic neuropathy: Distal paraesthesia and hypaesthesia; occasional Lhermitte's phenomenon Distal hypo or areflexia	*Chronic neuropathy:* Rare distal weakness	–	23, 24, 26–28	272
Thalidomide	Painful paraesthesia, burning sensation, numbness and hypaesthesia Distal hypo or areflexia	Proximal or distal LL weakness, tremor and cramps	–	29–34	107
Bortezomib	Painful paraesthesia, aching, burning, cold pain or allodynia, numbness and hypaesthesia Distal hypo or areflexia	Rare	Postural hypotension, gastrointestinal disturbance	35–40	410

Key: *N–Cumulative patient numbers from all the papers referenced; Ref–References: 1 McLeod and Penny (1969); 2 Bradley et al. (1970); 3 Casey et al. (1973); 4 DeAngelis et al. (1991); 5 Pal (1999); 6 Chen et al. (2013); 7 Lipton et al. (1989); 8 Pace et al. (1997); 9 Openshaw et al. (2004); 10 Augusto et al. (2008); 11 Park et al. (2011a); 12 Cavaletti et al. (1995); 13 Thompson et al. (1984); 14 Boogerd et al. (1990); 15 LoMonaco et al. (1992); 16 Sghirlanzoni et al. (1992), 17 Fu et al. (1995); 18 Bogliun et al. (1997); 19 Roelofs et al. (1984); 20 Krarup-Hansen et al. (2007); 21 Krishnan et al. (2005); 22 Wilson et al. (2002); 23 Park et al. (2009c); 24 Park et al. (2011c); 25 Argyriou et al. (2013); 26 Argyriou et al. (2007a); 27 Briani et al. (2014); 28 Taieb et al. (2002); 29 Plasmati et al. (2007); 30 Wulff et al. (1985); 31 Lagueny et al. (1986); 32 Chaudhry et al. (2002); 33 Isoardo et al. (2004); 34 Ochonisky et al. (1994); 35 Lanzani et al. (2008); 36 Rampen et al. (2013); 37 Richardson et al. (2006); 38 Velasco et al. (2010); 39 Ravaglia et al. (2008); 40 Thawani et al. (2015).