RM Partners
West London Cancer Alliance

Hosted by The Royal Marsden NHS Foundation Trust

NHS

Chemotherapy-induced Peripheral Neuropathy

Treatment Guidelines June 2019

Contents

1 Introduction

As the incidence of cancer rises, and treatment becomes more effective, increasing numbers of people are living with and beyond their cancer diagnosis. While many will return to their previous levels of health and well-being, a significant number will develop consequences of this illness and its treatment, either during or soon after treatment completion, or in some cases many years later. These consequences can have a serious impact on people's quality of life and their ability to participate in activities which are important to them. It is becoming increasingly clear that there need to be clear pathways for the assessment, management and, when necessary, onward referral of these consequences in order to support people to 'live well' beyond their cancer treatment.

2 Overview and Rationale

Mapping surveys of cancer treatment-induced peripheral neuropathy management within RM Partners showed that peripheral neuropathy and its treatment are often raised during oncology consultations. However, most oncology healthcare professionals have not received additional training to help them discuss and manage this condition.

As a result of this mapping, clear pathways for the assessment, management and onward referral of peripheral neuropathy have been developed to support people to access services currently available.

These guidelines are syntheses of the best available evidence and are designed to support decision making in practice.

3 Method

The Peripheral Neuropathy Working Group, under the remit of the RM Partners Living With and Beyond Cancer (LWBC) Pathway Group, completed two concurrent mapping exercises to identify:

- Current peripheral neuropathy management within oncology services
- Peripheral neuropathy-related learning needs of oncology healthcare professionals
- Prevalence of sexual consequences identified within different primary diagnostic groups
- Capacity within pain clinics, neurology clinics and amongst specialist occupational therapists and physiotherapists to provide intervention for people living with peripheral neuropathy as a consequence of cancer and its treatment.

These mapping surveys provided further evidence to the expert consensus within the working group that clear, evidence-based guidance was needed to support healthcare professionals to offer the most appropriate interventions to people living with and beyond cancer.

The working group met with interdisciplinary core working group representation from pain clinics, occupational therapists, physiotherapists and medical oncology.

Working group meetings were used to discuss and reach consensus on the scope, evidence base and operational detail of the guidelines and management pathways prior to wider consultation through RM Partners LWBC and tumour-specific working groups. Final approval was sought at the Clinical Oversight Group prior to RM Partners dissemination.

4 Causes of Peripheral Neuropathy

Peripheral neuropathy (PN) may be caused by the cancer, either by chemicals it releases such as in multiple myeloma, when the myeloma cells produce paraprotein which can deposit in the nerves, causing damage to the nerve cells, or it may be a result of direct pressure of the cancer itself on a nerve.

It is more commonly a consequence not of the cancer per se but of the cancer treatment encompassing surgery, radiotherapy or chemotherapy. Surgical causes of PN include operations on the lung or breast causing damage to nerves in the chest and underarm areas, which can lead to neuropathic symptoms such as pain, numbness, tingling, and/or increased sensitivity in those areas. The occurrence of radiation-induced peripheral neuropathy is rare, usually appearing several years after radiotherapy but symptoms can be progressive and usually irreversible. Whilst the site of nerve damage from both surgery and radiation can be predicted, the likelihood of it occurring and impact on long-term quality of life cannot.

This guidance will focus on chemotherapy-induced peripheral neuropathy (CIPN) since it is a particularly common consequence of this treatment; it is estimated to be approximately 38% in patients treated with multiple agents. The likelihood that CIPN develops is dependent on the drugs used; those most commonly associated with CIPN being the platinum drugs, vinca alkaloids, bortezomib, and/or taxanes. The most common tumour groups affected by CIPN include breast, colorectal, ovarian and haematology.

5 Types of Peripheral Neuropathy

There are three different types of peripheral neuropathy:

- Sensory neuropathy – this leads to loss of temperature, increased pain and altered pressure sensations.
- Autonomic neuropathy – this leads to changes in sweat glands, moisture and texture in the skin. There can also be an inability to control muscles that expand or contract blood vessels to maintain safe blood pressure levels. This can lead to a lowered blood pressure with symptoms of dizziness, light-headedness, or even fainting when a person moves suddenly from a seated to a standing position. If the nerves located in the gut are affected then this can lead to diarrhoea, constipation or incontinence.
- Motor neuropathy – this can lead to a loss of motor function, muscle weakness, decreased foot stability, painful cramps, muscle wasting and altered foot structure.

CIPN predominantly consists of sensory symptoms, rather than motor ones, which are dose dependent. As chemotherapy cycles are delivered, symptoms get progressively worse. Recent studies put the prevalence of CIPN at approximately 68.1% when measured in the first month after chemotherapy, 60.0% at 3 months, and 30.0% at and after 6 months [1]. However, signs and symptoms may continue to develop and progress for an additional 2 to 6 months post-therapy. In the case of oxaliplatin-induced peripheral neuropathy, symptoms will completely resolve in about 40% of people affected 6 to 8 months after cessation of treatment. Paclitaxel-induced peripheral neuropathy also improves in most patients in the months after cessation of treatment, but continues to be a prominent long-term problem in a subset of patients. By contrast, motor nerve function consistently remains unchanged during treatment with most neurotoxic agents.

One of the challenges in managing and preventing CIPN is that the exact pathophysiology is not well understood. What we do know is that the course of CIPN can be unpredictable, and although some symptoms may improve with time, others may continue or worsen as a result of permanent nerve damage.

Prompt and accurate cancer symptom management is important as persistent, unrelieved symptoms interfere with activities of daily living, can affect emotional well-being and impair quality of life (QoL).

6 Assessment of Chemotherapy-induced Peripheral Neuropathy

6.1 Introduction

- Assessment of CIPN is crucial for early identification and improved management.
- Assessment should be encouraged pre-chemotherapy, post each cycle and during post-chemotherapy surveillance.
- Assessment of CIPN involves establishing whether pain is associated with the neuropathy, the site and severity of any changes in sensation, presence and degree of alteration in motor function and degree of any functional impairment.
- There are numerous and varied tools for assessment of CIPN but at present there is no accepted standard for what tools to use or questions to ask.
- Painful CIPN is a type of neuropathic pain and use of a neuropathic pain tool may be useful.
- There has also been a move towards using patient-based assessments to support a patient centred and individualised approach to its management in this population. This is important as CIPN can impair quality of life [2].

6.2 Barriers to assessment

There are several barriers to effective assessment of CIPN both patient and practitioner related:

- People with CIPN may fear that its disclosure will result in dose modification or chemotherapy cessation.
- The lack of effective preventative strategies or treatments for CIPN may foster reluctance by practitioners to investigate it fully.

6.3 Assessment

A complete patient history and examination is pivotal in the diagnosis of CIPN, which should be combined with other assessment tools. Assessment of CIPN can be categorised by the focus of that assessment:

1) Diagnosis and differential diagnosis

Peripheral neuropathy has many potential causes; non-cancer causes include diabetes, chronic kidney disease, and hypothyroidism. Differential diagnosis will be established through conducting a full medical history and physical examination which may include blood tests, imaging tests, nerve function tests such as electromyography and possibly nerve biopsy.

2) Severity of CIPN and degree of functional impairment

Many of the CIPN-specific assessment tools primarily measure severity. Assessment of functional impairment is key to a patient-centred approach.

3) How these variables may change with time and/or treatment

Assessment and re-assessment is critical and some tools may be able to detect change.

6.3.1 History

Evidence of previous neuropathy either from (i) previous chemotherapy or (ii) other aetiology such as diabetes, alcohol use. The history should include:

Details of chemotherapy regimen

- Dose and cumulative dose, number of cycles
- Onset of symptoms in relation to chemotherapy
- Coasting assessment (when neuropathy occurs or worsens after cessation of chemotherapy)
- Evidence of change over time (better or worse)

Symptoms

- Distribution (hands, feet, or more proximal)
- Numbness, paraesthesia, pain (spontaneous or evoked)
- Motor or sympathetic dysfunction
- Functionality and interference on activities

6.3.2 Examination

Some degree of sensory testing should be attempted (see notes in Specific assessment tools section 6.3.4) but will be influenced by experience, equipment and time limitations. Assessments of sensations to the following are recommended:

- light touch
- pin prick or painful stimulus
- vibration sense
- cold/hot sensation

6.3.3 Pain and neuropathic pain assessment

There is value in using a validated assessment tool which is person-centred, since significant discrepancies have been demonstrated between patient and doctor assessments [3].

General pain assessments, such as the McGill pain questionnaire (MPQ) [4], and the short form version (MPQ-SF) [5] can measure pain severity and have been validated in this population [6]. The Brief Pain Inventory (BPI) also assesses pain severity ('sensory' dimension) but also considers the impact on function ('reactive' dimension). The BPI also has a short form that benefits from brevity without compromising utility [7]. The inclusion of a functional aspect in the BPI lends strength to the recommendation for its use for CIPN.

Tools exist to identify neuropathic pain (of which painful CIPN is one exemplar) although do not address the underlying aetiology. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) is well validated and the self-report version S-LANSS allows it to be patient-centred [8].

Several other neuropathic pain assessments exist (such as painDETECT and DN4) and may have differential merits as regards specificity and sensitivity for certain types of neuropathic pain in cancer pain [9]. It was suggested that painDETECT had very low sensitivity in this population.

There is no specific evidence to support the choice of one over the others in CIPN.

CIPN cannot be considered a homogenous entity since the underlying mechanisms and presenting pain phenotype can be markedly different between the neurotoxic chemotherapies and even within CIPN induced by a single agent. This questions how sensitive and specific a general CIPN assessment tool can be and whether agent-specific CIPN assessment tools should be developed. So far there few such validated tools available.

6.3.4 Specific assessment tools for CIPN

At present there is insufficient evidence and not enough fully validated assessments to recommend these tools; however they may be useful in some instances.

One such specific scale (the oxaliplatin grading scale) has been used for assessment of CIPN secondary to taxanes, vinca alkaloids and platinum compounds. This scale is one of the few tools to include a durations of symptoms assessment [10].

Some previously used assessment tools have been limited by several factors including being purely clinician completed and not involving assessment of pain or impact on activities of daily living or quality of life. Moreover, comparison of four such severity scales for CIPN – WHO, ECOG, NCIC-CTC and Ajani – showed that there was little inter-observer agreement of grading [11]. Therefore tools should be chosen that minimise such inadequacies.

FACT/GOG-NTX

- FACT/GOG-NTX uses questions that ask asking physical, social/family, emotional and functional well-being, with an additional 11 questions specifically asking about neuropathy (also referred to as the FACT/GOG-NTX subscale). This subscale is widely used alone and has validity not only for assessment but also to monitor change with time [12].
- A shortened version of the FACT/GOG-NTX subscale using 4 questions instead of 11 has also been shown to be as reliable for paclitaxel/cisplatin-induced CIPN [13].

- There is also some evidence that suggests the FACT/GOG-NTX assessment is more sensitive than QST [14].
- Although FACT/GOG-NTX was formulated for patients with gynaecological malignancies and certain chemotherapies, many aspects of CIPN assessment are pertinent to other chemotherapies and oncological disease. Furthermore the ability to monitor changes in CIPN with time has significant merit.

Patient Neurotoxicity Questionnaire (PNQ)

- The PNQ has been suggested as a valid tool for CIPN assessment and fulfils the remit for using patient-centred assessments as well as having a high level of completion compliance. Comparison with the National Cancer Institute Common Toxicity Criteria (NCI-CTC), which is a more practitioner-reported outcome, showed NCI-CTC tended to under report neurosensory symptoms [15].

Quality of Life scales

- One tool developed by the European Organization of Research and Treatment of Cancer (EORTC) that has been designed to assess quality of life in the CIPN population is the Quality of Life Questionnaire-CIPN 20-item scale (QLQ-CIPN20) [16].
- This patient-centred 20 question assessment was found to be reliable for several aetiologies of CIPN and sensitive enough to pick up quality of life issues important to the patient but not assessed satisfactorily by other tools.
- A shorter 16 question version would be as valid and still as sensitive for assessment of CIPN [17].

QST, nerve conduction and skin biopsy

Quantitative sensory testing (QST) can give some mechanistic insight to CIPN and provide a detailed sensory phenotype [18]. However, QST requires specialist training and equipment but also is potentially overly time-consuming for routine use in clinics (and is not generally reimbursed by medical insurers). Moreover, there is at present little evidence that QST can detect subclinical changes that would be an early indicator of subsequent symptomatology [19].

In another study of paclitaxel-induced neuropathy, 71% complained of paraesthesia but only 48% showed QST changes [20]. Nevertheless where time, expertise and equipment are available, QST can provide the most comprehensive mechanistic evaluation. Simplified sensory testing could mitigate some of these concerns.

Sensory nerve conduction studies measure myelinated sensory nerve function and may reflect overall sensory nerve damage but give little insight into fibre function that is responsible for many other signs and symptoms. Use of nerve conduction studies may be considered on an individual basis but does not form part of the key CIPN assessments. Test of vibration sense at the ankle may be a proxy measure of general sensory nerve damage and is a simple and inexpensive element of QST [21].

Epidermal nerve fibre loss (diagnosed by skin biopsy) is thought to be a common end result of many types of CIPN and may have some merit in the diagnosis of CIPN [22]. However, these changes often occur after symptoms are experienced, and routine skin biopsy cannot be recommended.

6.3.5 Suggested CIPN assessment schedule

There are three key stages at which assessment should be conducted:

Pre-chemotherapy

- Baseline assessment is crucial since the incidence of pre-existing CIPN is high, often secondary to previous neurotoxic chemotherapies.

After each cycle

- Repeated assessment after each cycle (or before the next) will allow timely diagnosis of new or worsening CIPN.

Post chemotherapy surveillance

- Some cases of CIPN first occur or worsen after the cessation of chemotherapy therefore later assessment is recommended. Although most sensory loss occurs usually within three months of cessation of treatment (often referred to as coasting) anecdotal reports suggest occasionally CIPN may present even longer after stopping chemotherapy. Furthermore, CIPN can persist and longer term surveillance will aid identification of survivors with longer term pain issues.
- At each stage, there are both general and specific CIPN assessment tools which are recommended and others whose use can be considered optional (see table on page 10).

6.3.6 Summary

Assessment is critical to prompt and appropriate management of CIPN. It is the responsibility of all practitioners prescribing and administering chemotherapy as well as those supporting these individuals through such treatment to assess for CIPN. A range of validated general and CIPN specific assessment and grading scales for this patient population are highlighted and their use is recommended before, during and after treatment.

Assessment of Chemotherapy-Induced Neuropathy and Neuropathic Pain

	General assessments			Specific CIPN assessments			Other assessments		
Assessments	BPI	Neuropathic pain assessment (LANSS or DN4)	Quality of life (QLQ-CIPN16)	FACT/GOG-NTX	PNQ	WHO/Ajani/NCIC-CTC and other CIPN assessments*	QST**	Epidermal nerve fibre density	Nerve conduction studies
Pre-chemotherapy	✓	✓	✓	✓	✓	—	—	—	X
Before each cycle of chemotherapy	✓	✓	✓	✓	✓	—	—	—	X
After chemotherapy surveillance	✓	✓	✓	✓	✓	—	—	—	X

Recommended ✓ Optional — Not recommended X

*Other non-CIPN elements of WHO or NCIC-CTC may be applicable.

** Malleolar vibration (@256Hz) may serve as a general indicator of global sensory status.

7 Treatment Recommendations

The American Society of Clinical Oncology (ASCO) produced evidence-based guidance on the optimum prevention and treatment approaches in the management of CIPN in adult cancer survivors [23]. This guidance, published in 2014, still offers the most comprehensive review of treatments for this condition. ASCO reviewed a total of 42 studies which provided information on 19 different interventions for the prevention of CIPN; 6 studies provided information on 6 different agents evaluated in treatment of established neuropathy.

7.1 Prevention recommendations

Some studies have investigated whether vitamin or mineral supplementation, in particular intake of an oral B group vitamin, may be a useful adjunct to neurotoxic chemotherapy regimens but there is insufficient evidence to support this. Due to lack of high-quality, consistent evidence, these guidelines do not recommend any agents for use in prevention of CIPN.

To date there are no reliable genomic biomarkers to predict CIPN.

7.2 Treatment recommendations

ASCO's systematic review did provide a moderate strength recommendation for treatment of CIPN with duloxetine (intermediate strength of evidence, moderate evidence of efficacy, and low evidence of harm).

No recommendations (recommendation = inconclusive) were made on the use of the following agents, although the guidelines consider it reasonable to try tricyclic antidepressants, gabapentin, and a topical gel treatment containing baclofen, amitriptyline, and ketamine in select patients:

- Acetyl-L-carnitine (low strength of evidence, low evidence of efficacy, moderate evidence of harm). The guidelines note that an abstract for a phase III trial supported its value, but the trial has yet to be published in a peer-reviewed journal, and a prevention trial suggested worse outcomes with this agent.
- Tricyclic antidepressants (e.g. nortryptyline/amitriptyline; intermediate strength of evidence, low evidence of efficacy and harm). The guidelines state that given limited options in CIPN and efficacy of these drugs in other neuropathic pain conditions, it is reasonable to try a tricyclic antidepressant (e.g. nortriptyline or desipramine) in treatment.
- Gabapentin (intermediate strength of evidence, low evidence of efficacy and harm). The guidelines state that it is reasonable to try this agent in select patients with CIPN pain, based on the fact that only one negative randomised trial for this agent was completed and given the efficacy of gabapentin and pregabalin in other forms of neuropathic pain.
- Topical gel treatment containing baclofen (10mg), amitriptyline (40mg), and ketamine (20mg) (intermediate strength of evidence, moderate evidence of efficacy, and low evidence of harm). The guidelines note that a single trial supported a reduction in CIPN symptoms with this treatment and that it is reasonable to try the treatment in select patients with neuropathic pain.

For tricyclic antidepressants, gabapentin, and the compounded topical gel, use should occur after discussion with patients about the limited evidence of efficacy in CIPN, potential harms and

benefits, cost, and patient preferences. The guidelines state that further research on use of these agents in CIPN is warranted.

The guidelines make a moderate recommendation against use of lamotrigine (intermediate strength of evidence, no evidence of efficacy, and low evidence of harm) in treatment of CIPN.

8 Patient Support and Information

8.1 Managing distress

Understanding how a patient's QoL is impacted by treatment can provide critical information that may help in determining the best treatment for that individual. CIPN can cause symptoms which are debilitating, in particular pain and loss of sensation, which impact on an individual's daily functioning.

Patients can find it concerning that the course of CIPN can be unpredictable, as whilst their symptoms may resolve after the chemotherapy is discontinued, they may also continue for some years.

The section on assessment of CIPN above (Chapter 6) covers how best to measure symptom severity but it is also important to understand symptom distress in order to fully understand the symptom experience. In some cases, symptom severity and symptom distress may not correlate with each other, and thus, the most severe symptoms may not present as the most distressing.

Another cause for distress is that if CIPN arises during treatment it can result in chemotherapy dose reduction or discontinuation, and individuals can feel very concerned about how this might affect their overall survival. For this reason inherent in this education is teaching the patient and family about common patient-related barriers, including the importance of reporting CIPN and not waiting for providers to introduce the subject first.

8.2 Patient education

The patient and family should receive education about CIPN and common strategies for its management.

- Protecting hands and feet

If their hands or feet are affected, it's important to protect them as much as possible:

- Keep warm by wearing gloves and socks in cold weather.
- Wear gloves when working with hands, for example, when gardening or washing up.
- Use pot holders and take care to avoid burning hands when cooking.
- Wear well-fitting shoes or boots.
- Avoid walking around barefoot and check feet often for any problems.
- If balance, coordination or walking is affected, they may be more at risk of accidents and falls.
- Make sure rooms are well lit and always put a light on during the night.
- Keep areas free of clutter. Make sure there aren't things (such as loose rugs) that they could trip over.
- Get advice from a physiotherapist about walking aids if balance is affected.

- Feeling lightheaded or dizzy

The GP can give advice if problems with blood pressure are causing the individual to feel lightheaded or dizzy when they stand up. The following suggestions may also help:

  - Support stockings can improve circulation and help symptoms.
  - Performing leg exercises, such as moving feet up and down at the ankle and some gentle marching on the spot, before standing up can help.
  - Standing up more slowly, as this gives the body more time to adjust to the change in position.
  - Drinking plenty of fluids. Being dehydrated can make symptoms worse.

- Problems with constipation
  - If there are also problems with constipation, review fibre and fluid intake, consider use of laxatives and encourage them to try to keep active.

9 Rehabilitation and Adaptation

Patients with CIPN report high levels of functional disability, poorer quality of life and increased number of falls [24, 25]. Patients report reduced independence with completion of basic day to day activities such as personal care (e.g. difficulty with fine motor tasks such as fastening buttons), domestic tasks, as well as difficulties with balance, coordination and walking [26, 27].

Occupational therapy and physiotherapy assessment and intervention has been shown to reduce the impact of CIPN on daily life and maximise functional independence [25, 26].

As previously described, assessment and treatment for CIPN requires a multidisciplinary approach, including detailed assessment of motor function, sensation, pain, range of movement, the impact on quality of life and function within day to day tasks.

Broadly speaking, occupational therapy interventions focus on adaptation (e.g. use of equipment or compensatory strategies to maximise functional independence) and remediation (e.g. fatigue management education, hand and arm exercises), while physiotherapy intervention can provide advice on tailored exercise programmes to improve muscle strength and more specific interventions such as acupuncture to reduce neuropathic pain [28].

Key areas for therapy intervention following CIPN include:

- falls and mobility deficits
- sensory deficits and pain
- functional impairment

9.1 Falls and mobility deficits

Research has shown that patients receiving chemotherapy are at increased risk of falls and that with each cycle of chemotherapy the risk of falls increases [29]. Symptoms of CIPN including strength deficits, reduced sensation, and reduced proprioception in conjunction with fatigue, can cause difficulties with walking, balance and coordination – increasing the risk of falls.

Occupational therapy assessment and adaptation of the home environment may be beneficial to provide practical advice on reducing the risk of falls such as ensuring the environment is well lit, free from potential trip/fall hazards as well as advice on fatigue management and energy conservation techniques. Adaptive equipment may be beneficial to support fatigue management strategies, e.g. a perching stool for tasks requiring long periods of standing.

Physiotherapy intervention may include more detailed assessment of muscle strength, balance and mobility using tools such as the Berg Balance Test, the Timed Up and Go and Single Leg Stance [24]. Physiotherapy intervention can also include provision of mobility aids.

While there is currently no evidence directly supporting the role of exercise in improving CIPN symptoms, research has shown that exercise to strengthen muscles can help to reduce falls, improve functional independence and overall quality of life through improving muscle strength [29].

9.2 Sensory deficits and pain

As previously described, detailed sensory assessment and assessment of pain are an integral component of assessment and intervention for CIPN. Occupational therapy and physiotherapy can provide advice and education on maintaining safety in functional tasks (foot and hand safety) with sensory impairments and skin care. Practical advice on protecting the hands and feet (as also described in the Patient Education section 8.2) can include wearing gloves when working with the hands (e.g. for washing up or gardening); wearing well-fitting shoes; wearing gloves and socks in cold weather; testing the temperature of hot water (e.g. bath, shower, washing up) with the elbow rather than hand to reduce the risk of burns.

As well as pharmaceutical pain relief, there is some evidence for the use of acupuncture, reflexology, transcutaneous electrical nerve stimulation (TENS) and sonopuncture (vibration) in managing the symptoms of CIPN [31, 32]. Several studies to date have shown functional and subjective improvements in CIPN with acupuncture with no adverse effects [30]. However a recent Cochrane review has concluded that there is insufficient evidence to support or refute the use of acupuncture in treating neuropathic pain [33].

9.3 Functional impairment

In addition to falls, studies have highlighted that patients experiencing symptoms of CIPN report difficulties with completing domestic tasks such as laundry and housework; personal care tasks including bathing; and community tasks such as shopping, money management and outdoor mobility [24].

Therapy provision of adaptive equipment may be beneficial to maintain independence, e.g. use of mobility aids, equipment for the bath or home. Advice and education regarding the principles of energy conservation and fatigue management may also be beneficial such as planning the day’s activities to reduce exertion and fatigue, scheduling regular rest breaks, utilising good working heights and equipment to reduce fatigue.

Assessment of fine motor tasks and coordination may also be beneficial.

While further research is indicated for specific therapeutic interventions to alleviate the symptoms of CIPN, occupational therapy and physiotherapy are key components of a multidisciplinary approach to maintaining functional safety and independence.

10 Physical Activity

A personalised programme of physical activity can be offered as a treatment for any functional impairments resulting from CIPN. The weakness, fatigue, and neuromuscular deficits often seen in CIPN can be treated with exercises aimed at strengthening muscles and improving proprioceptive stimulation, fine motor and gross motor coordination and balance [25].

A comprehensive physical activity routine might therefore include four kinds of activities:

- Aerobic exercise
- Flexibility exercise
- Strength training exercise
- Balance exercise

These interventions may be used for neuropathy felt in both feet and fingers.

For those with altered balance due to CIPN-related pain and paraesthesia, activities which improve static and dynamic balance and increase lower limb strength might reduce the likelihood of a fall [34]. Further evaluation of the benefits of physical activity is needed in this patient group [35].

11 Summary

Peripheral neuropathy is viewed by those affected by it, their carers and by some professionals as a challenging consequence of cancer and its treatment. The sections in these guidelines highlight the steps healthcare professionals need to take to manage this common consequence of chemotherapy-induced peripheral neuropathy: prevention, assessment, treatment, patient support and rehabilitation. In addition, education for all stakeholders is an integral part of any prospective plan for CIPN management. Improved understanding is essential to advance CIPN management.

12 References

1. Seretny M., Currie G.L., Sena E.S. (2014) Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain. 2014;155:2461–2470.
2. Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L. (2014) Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. Support Care Cancer 22(8):2261-9.
3. Stephens RJ, Hopwood P, Girling DJ, Machin D. (1997) Randomized trials with quality of life endpoints: are doctors' ratings of patients' physical symptoms interchangeable with patients' self-ratings? Qual Life Res. 6:225-238.
4. Mazak R. (1975) The McGill Pain Questionnaire: major properties and scoring methods. Pain1(3):277-99.
5. Melzack R. (1987) The short-form McGill Pain Questionnaire Pain 30(2):191-7.
6. Ngamkham S, Vincent C, Finnegan L. et al (2012) The McGill Pain Questionnaire as a multidimensional measure in people with cancer: an integrative review. Pain Manag Nurs. 13(1):27-51
7. Cleeland CS, Ryan KM. (1994) Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 23(2):129-38.
8. Pérez C, Sánchez-Martínez N, Ballesteros A. et al (2015) Prevalence of pain and relative diagnostic performance of screening tools for neuropathic pain in cancer patients: A cross-sectional study. Eur J Pain19(6):752-61.
9. Postma TJ, Heimans JJ, Muller MJ, et al. (1998) Pitfalls in grading severity of chemotherapy-induced peripheral neuropathy. Ann Oncol 9:739–744.
10. Kautio AL, Haanpää M, Kautiainen H,et al. (2011) Oxaliplatin scale and National Cancer Institute-Common Toxicity Criteria in the assessment of chemotherapy-induced peripheral neuropathy. Anticancer Res. 31(10):3493-6.
11. Calhoun EA, Welshman EE, Chang CH.(2003) Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. Int J Gynecol Cancer 13(6):741-8.
12. Huang HQ, Brady MF, Cella D, Fleming G. (2007) Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. Int J Gynecol Cancer 17(2):387-93.
13. Hershman DL, Weimer LH, Wang A, Kranwinkel G, Brafman L, Fuentes D, Awad D, Crew KD. (2011) Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. Breast Cancer Res Treat. 125(3):767-74.
14. Shimozuma K, Ohashi Y, Takeuchi A. et al (2009) Feasibility and validity of the Patient Neurotoxicity Questionnaire during taxane chemotherapy in a phase III randomized trial in patients with breast cancer: N-SAS BC 02. Support Care Cancer 17(12):1483-91.
15. Postma TJ, Aaronson NK, Heimans JJ et al EORTC Quality of Life Group. (2005) The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. Eur J Cancer. 41(8):1135-9.
16. Lavoie Smith EM, Barton DL, Qin R. et al(2013) Assessing patient-reported peripheral neuropathy: the reliability and validity of the European Organization for Research and Treatment of Cancer QLQ-CIPN20 Questionnaire. Qual Life Res. 22(10):2787-99.

17. Lavoie Smith, E. M., Haupt, R., Kelly, et al. (2017). The Content Validity of a Chemotherapy-Induced Peripheral Neuropathy Patient-Reported Outcome Measure. *Oncology nursing forum*, *44*(5), 580–588.
18. Baron R, Maier C, Attal N, et al German Neuropathic Pain Research Network (DFNS), and the EUROPAIN and NEUROPAIN consortia. (2017) Peripheral Neuropathic Pain: A mechanism-related organizing principle based on sensory profiles. Pain. 158(2): 261–272.
19. Forsyth PA, Balmaceda C, Peterson K. et al (1997) Prospective study of paclitaxel-induced peripheral neuropathy with quantitative sensory testing. J Neurooncol. 35(1):47-53.
20. du Bois A, Schlaich M, Luck HJ, et al. (1999) Evaluation of neurotoxicity induced by paclitaxel second-line chemotherapy. Support Care Cancer 7:354–361.
21. Hershman DL, Weimer LH, Wang A. (2011) Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. Breast Cancer Res Treat. 125(3):767-74.
22. Han Y, Smith MT. (2013) Pathobiology of cancer chemotherapy-induced peripheral neuropathy (CIPN). Front Pharmacol. 4:156.
23. Hershman DL, Lacchetti C, Dworkin RH, et al: (2014) Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 32 (18): 1941-1967.
24. Cheville, A., Beck L, Petersen T (2009) The Detection and Treatment of Cancer Related Functional problems in an out-patient setting. Support Care Cancer 17: 61-67.
25. Pergolotti M, Williams G, Campbell C, Munoz L, Muss, H (2016) Occupational Therapy for Adults with Cancer: Why it Matters. The Oncologist 21:1-6.
26. Veale, P. (2016) Rehabilitation Management for Chemo-Induced Peripheral Neuropathy. Available at: http://www.rehabpub.com/2016/08/rehabilitation-management-chemo-induced-peripheral-neuropathy/ (accessed 10th January, 19)
27. Wonders K, Stout, B. (2016) The Role of Exercise in Chemotherapy Induced Peripheral Neuropathy Chapter 19: in Neuro-Oncology- Newer developments. Edited by Agrawal, A. (2016) In tech Open.
28. Tofthagen C, Overcast J, Kip K. (2011) Falls in Persons with Chemotherapy induced Peripheral Neuropathy. Support Care Cancer 20 (3) 583-589.
29. Pachman D, Watson J, Lustberg M. (2014) Management Options for established chemotherapy induced peripheral neuropathy. Support Care Cancer 22 (8) 2281-2295.
30. Franconi G, Manni L, Schröder S. et al (2013) A systematic review of experimental and clinical acupuncture in chemotherapy-induced peripheral neuropathy. Evid Based Complement Alternat Med. 2013:516-916.
31. Ben-Horin I, Kahan P, Ryvo L. et al (2017) Acupuncture and Reflexology for Chemotherapy-Induced Peripheral Neuropathy in Breast Cancer. Integr Cancer Ther.;16(3):258-262.
32. Kurt S, Can G. (2018) Reflexology in the management of chemotherapy induced peripheral neuropathy: A pilot randomized controlled trial. Eur J Oncol Nurs.; 32:12-19.
33. Ju ZY, Wang K, Cui HS. et al ((2017) Acupuncture for neuropathic pain in adults. Review. Cochrane Library Issue 12. Art. No.: CD012057. DOI: 10.1002/14651858.CD012057.pub2
34. Brayall, P. Donlon, E. Doyle, L. et al (2018) Physical Therapy–Based Interventions Improve Balance, Function, Symptoms, and Quality of Life in Patients With Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review. Rehabilitation Oncology: 36 (3) 161–166

35. F. Duregon, B. Vendramin, V. Bullo, S. et al (2018) Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review Crit. Rev. Oncol. Hematol. 121:90-100,

13 Further Reading

https://www.beatingbowelcancer.org/how-we-can-help/booklets-factsheets

http://www.macmillan.org.uk/information-and-support/coping/side-effects-and-symptoms/other-side-effects/peripheral-neuropathy.html

https://www.foundationforpn.org/

https://www.foundationforpn.org/what-is-peripheral-neuropathy/causes/chemo-induced-pn/

http://www.cancersupportivecare.com/nervepain.php

http://oncologypt.org/pdfs/fact-sheets/CIPN-Factsheet.pdf

https://www.livestrong.org/we-can-help/finishing-treatment/neuropathy

http://www.myturningpoint.org/files/CIPN_Patient_Handout.pdf

https://www.nccn.org/patients/resources/life_with_cancer/managing_symptoms/neuropathy.aspx

http://chemocare.com/chemotherapy/side-effects/numbness-tingling.aspx