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Chemotherapy-induced peripheral neuropathy (CIPN): where are we now?

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Abstract

Chemotherapy induced peripheral neuropathy (CIPN) is a major challenge, with increasing impact as oncological treatments, using potentially neurotoxic chemotherapy, improve cancer cure and survival. Acute CIPN occurs during chemotherapy, sometimes requiring dose reduction or cessation, impacting on survival. Around 30% of patients will still have CIPN a year, or more, after finishing chemotherapy.

Accurate assessment is essential to improve knowledge around prevalence and incidence of CIPN. Consensus is needed to standardize assessment and diagnosis, with use of well validated tools, such as the EORTC-CIPN 20. Detailed phenotyping of the clinical syndrome moves towards a precision medicine approach, to individualize treatment. Understanding significant risk factors and pre-existing vulnerability may be used to improve strategies for CIPN prevention, or to use targeted treatment for established CIPN.

No preventive therapies have shown significant clinical efficacy, although there are promising novel agents such as histone deacetylase 6 (HDAC6) inhibitors, currently in early phase clinical trials for cancer treatment. Drug repurposing, e.g. metformin, may offer an alternative therapeutic avenue. Established treatment for painful CIPN is limited. Following recommendations for general neuropathic pain is logical, but evidence for agents such as gabapentinoids and amitriptyline is weak. The only agent currently recommended by the American Society of Clinical Oncology is duloxetine.

Mechanisms are complex with changes in ion channels (sodium, potassium and calcium), Transient Receptor Potential (TRP) channels, mitochondrial dysfunction, and immune cell interactions. Improved understanding is essential to advance CIPN management. On a positive note, there are many potential sites for modulation, with novel analgesic approaches.

Introduction

Chemotherapy induced peripheral neuropathy (CIPN) is a common and challenging complication arising from treatment with many commonly used anti-cancer agents. A number of factors have contributed to the increasing prevalence of CIPN, including an increased incidence of cancer, with improved survival and cancer cure rates. CIPN can occur

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acutely, during chemotherapy. If severe, it can require a reduction in the dose of chemotherapy, or even stopping prior to completing the planned course[34; 45]. Clearly, this may have implications for efficacy of oncological treatment and survival. Whilst in many cases, acute CIPN will resolve after finishing chemotherapy, in a number of cases, it will persist, resulting in chronic symptoms, months, or even years later. In some cases, CIPN can emerge shortly after finishing chemotherapy, a phenomenon known as “coasting” [34]. For neurotoxic chemotherapy overall, the prevalence of CIPN 1 month after finishing chemotherapy is around 68%, with this dropping to 60% at 3 months and 30% at 6 months or more [88]. The type of chemotherapy does influence the risk of developing CIPN, although even with single chemotherapeutic agents there is often a wide range of reported occurrence (see table1). Some potential confounders that may affect the reported incidence or prevalence include how CIPN was defined and assessed; differing dosing regimens, assessment time point(s), and exclusion of participants with pre-existing neuropathy.

The clinical syndrome

CIPN develops as a glove and stocking neuropathy, although in more severe cases it can spread proximally affecting most of the limbs. Whilst it is predominantly a sensory neuropathy, autonomic function can also be affected, as can fine motor function and proprioception, with evidence for loss of sensory fibres and reduced intraepidermal nerve fibre density (IENFD)[8; 13; 15] [106]. Sensory dysfunction is wide ranging, with both positive and negative sensory signs, some of which are more often associated with particular types of chemotherapy e.g, cold hypersensitivity during platinum-based therapy. Neuropathic descriptors such as burning, and shooting are often used, along with numbness and paraesthesia, although pain is not always a presenting feature[42]. CIPN can persist for many years, with a detailed assessment of long term survivors of childhood cancers finding ~48% of individuals having some evidence of neuropathy: predominantly sensory dysfunction and reduced quality of life[51] Some of the clinical features of CIPN are shown in figure 1.

Assessment and diagnosis—Accurate assessment and diagnosis are not only the first steps in successful management, but are also important in understanding the epidemiology of CIPN. For painful CIPN, using a standard approach to neuropathic pain, the NeuPSIG guidelines for assessment and diagnosis of neuropathic pain can be applied. These guidelines recommend the use of screening questionnaires to identify potential patients, with a range of questionnaires available, many of which may not have been validated for CIPN [50]. Clinical examination is also an important part of assessment, but may have some challenges in non-specialist settings, particularly where using more detailed sensory profiling for definitive diagnosis[105] [44].

It could be argued, however, that painful CIPN is a particular case, with circumstances that require a more tailored approach than that used for general neuropathic pain:

- There is predictable delivery of a known toxic, but necessary, insult (chemotherapy) given repeatedly over the course of a number of weeks to months.

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- Completing the chemotherapy dosing regimen maximizes the chances of cancer survival, with any dosage modification impacting on this;
- Development of CIPN during treatment may necessitate dose reduction or cessation, with early identification of symptoms important in planning care;
- CIPN mechanisms may be specific to the chemotherapy given.

The approach to CIPN may therefore require a more “bespoke” assessment process that is designed to identify the particular characteristics of CIPN, as early as possible, to allow appropriate management (including potential alteration to the chemotherapy regimen). This has been recognised with the development of a number of screening tools specific for CIPN (see below).

Some have been developed for specific chemotherapeutic agents, such as the Functional Assessment of Cancer Therapy (FACT)–Taxane. This has been extensively validated, and is sensitive to change[38]. The EORTC-CIPN 20 can be used for any type of neurotoxic chemotherapy and has been rigorously studied. Some of the questions in the CIPN20 may potentially be less reliable – particularly those in the autonomic subscale, with the potential for reducing the length of the questionnaire without impacting on its performance. Rasch analysis revealed some inconsistencies, with evidence of a floor effect, and some issues with item scaling[95–97]. A reduced version of the CIPN20 – the CIPN 15 may address some of these concerns, with the added benefit of a reduced questionnaire burden on patients [96]. The Total Neuropathy Score (TNSc(©)) performs reasonably well, with a mix of clinician-detected signs and patient self report, but it doesn’t specifically assess pain. Rasch analysis revealed some inconsistencies with the 7 item tool, and has suggested a shortened 5 item version may perform better[11; 20].

One of the widely used clinical tools for detecting neuropathy during chemotherapy is the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE), but it is was not specifically developed to assess pain, is not sensitive to change and has significant inter-rater variability[19]. While many studies have used this to identify CIPN, particularly older studies, it is not a reliable assessment tool for clinical research, although may still have some clinical utility[35].

This lack of consistency in assessing CIPN has implications for accurate epidemiological studies, including those of risk factors[98]. This issue has been identified in several systematic reviews, where many different primary outcome measures (or combinations) were identified, with almost half of studies not even clearly defining a primary outcome measure[39; 88]. The need for a more uniform approach to assessment and diagnosis, in future studies, has been highlighted, although debate remains about the ideal tool to use [18; 37]. In clinical practice, a simple tool that can be used by non-specialists, to detect abnormalities early is needed. For research purposes, there is a need for a tool that performs consistently in different settings, with good reliability, sensitivity to change, detects key early symptoms of development (see figure 2).

Confirming a definitive diagnosis of CIPN does require more detailed phenotyping than a single assessment tool. Psychophysical testing is useful in the research setting, with the

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potential to use a modified approach for routine clinical use in the cancer setting [87; 107]. Nerve conduction studies are less sensitive at identifying CIPN than quantitative sensory testing (QST) with sensory fibres preferentially affected, although this may vary between chemotherapy type, and change as neuropathy develops. Decreases in IENFD correlated with altered QST, particularly for mechanical sensation, in patients with chronic CIPN after docetaxol or oxaliplatin [55]: After vincristine treatment, myelinated A-beta fibres were affected first, followed by A-delta and c fibres[29]. In patients with bortezomib induced CIPN no changes were identified in intraepidermal nerve fibre density, but there were clear reductions in subepidermal nerve fibre density of PGP9.5, with associated axonal swelling, and reduced sensory action potentials in the sural nerve[8]. Other studies of persistent CIPN after bortezomib, found a clear reduction in IENFD and Meissner's corpuscles, with associated abnormalities in QST[14]. These differences may be due to time point of testing, dosing regimen, or other factors, and emphasise the need for consistent approaches to assessment to give a detailed and accurate understanding of the natural history of CIPN.

Risk factors and vulnerability—Identifying who is at higher risk of developing CIPN would be an important step forwards. Large scale population based studies combined with careful phenotyping is a potential approach to this. Are certain individuals more vulnerable to the toxic insult of chemotherapy than others… and if so, how can we identify them?

A number of factors have been identified, associated with an increased risk of developing CIPN, although causal links are less clear (see table 2). Some of these are potentially modifiable, giving opportunities for using approaches to reduce CIPN development. Perhaps the most obvious ones are type and cumulative dose of chemotherapy, although here the challenge is to understand how alterations in dosing regimes might impact on cancer survival. Better understanding of this might allow a more individualised approach to chemotherapy dosing. For example, if individual is generally more sensitive to chemotherapy (i.e both toxic and therapeutic effects), it may be that reducing the dose does not impact on individual survival: this needs further study.

It may be possible to use detailed phenotyping to identify pre-existing vulnerability to developing CIPN. This approach is showing promise in some other areas, such as persistent post-surgical pain, [52; 61; 62; 100; 110]. QST has identified subclinical deficits in cancer patients prior to starting chemotherapy, compared to healthy controls, with those individuals showing the most marked deficits at higher risk of developing clinically significant CIPN. These findings were similar to a retrospective study of head and neck cancer patients, prior to starting chemotherapy, those with altered QST (and fine motor function) were at higher risk of developing CIPN [24; 83]. Predictors emerging during early chemotherapy have also been identified, with thermal hyperalgesia predicting development of severe oxaliplatin CIPN[5]. Our preliminary work, using functional neuroimaging, has also found structural and functional changes in the brain in pain processing areas, detected prior to starting chemotherapy, potentially indicating a pre-existing vulnerability to developing CIPN [89].

A number of studies have explored genetic factors in determining risk of developing CIPN. Studies using multivariate statistical modelling have identified several risk factors, including smoking, decreased creatinine clearance and baseline neuropathy, although there may be

some statistical bias introduced by the techniques used[5; 28; 88]. Informed by other Genome Wide Association Studies (GWAS), a study in more than 1000 patients with multiple myeloma identified 13 Single Nucleotide Polymorphisms (SNPs) associated with CIPN development, of which 4 were relevant for neural function[65]. A GWAS in breast cancer patients found that severe taxane related CIPN was associated with genes involved in diabetes and diabetic neuropathy, with the G allele of rs1858826 in GNGT1 decreasing CIPN risk[98]. A recent review of predictive biomarkers for CIPN found 3 genetic biomarkers that have been consistently identified in a number of studies: ARHGEF10 rs9657362 (neuronal morphogenesis), CYP2C8 rs11572080/rs10509681 (drug metabolism) and FGD4 rs10771973 (mutations found in Charcot-Marie tooth disease)[26]. Some studies have also found associations with genes associated with mitochondrial dysfunction, which may link with preclinical evidence for underlying mechanisms of CIPN development (see section below)[54].

CIPN Prevention—To date there are no preventive treatments for CIPN. This lack of any effective neuroprotective agents is a key area of unmet clinical need. While a number of trials having studied agents that may potentially modify CIPN development by targeting the underlying mechanisms, there is as yet insufficient evidence to recommend any specific agent[46]. There have been quite a number of CPIN prevention trials, many with small sample size, none of which have yielded high quality evidence. Agents that have been studied in clinical trials, often based on postulated effects on underlying mechanisms, include: Acetyl-L-carnitine (ALC)(associated with worse outcomes), amifostine, *N*-acetylcysteine, amitriptyline, nimodipine, glutathione, carbamazepine, Vitamin E, omega-3 fatty acids, or oxycarbazepine [2; 4; 46–48; 111]. Prevention trials face a number of design challenges, including whether to treat all patients receiving neurotoxic chemotherapy, accepting that some of them would not develop CIPN anyway. Not only does this increase the required sample size, but also exposes patients to a novel therapy unnecessarily. This is one area where identification for pre-existing vulnerability could improve clinical trial design. An alternative approach to prevention trials is to look at intervening when there are early (or subclinical signs of CIPN), using a detailed phenotyping approach[30; 37; 39; 63].

Treatment strategies—There is a lack of good quality clinical trials focusing on treatment of established painful CIPN, with a pragmatic approach extrapolating from evidence and guidelines for treatment of other types of neuropathic pain. Duloxetine is one of the few agents where there is a positive RCT in CIPN[94]. This is reflected in Clinical Practice Guidelines from ASCO, where duloxetine is the only treatment where there is sufficient evidence to recommend its use. However, based on efficacy in other neuropathic pain syndromes, other agents can be trialled, including tri-cyclic anti-depressants, gabapentin and topical gel (baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg),) that had limited positive evidence from one trial[46].

Non-pharmacological treatments may also be useful, although again with a mixed evidence base. A recent review of pharmacological strategies identified a number of current clinical trials of non-drug strategies, including exercise, acupuncture, massage, and nutritional interventions, not all of which were based on strong underlying hypotheses[21] An RCT of a

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6 week exercise programme showed small to moderate improvements in CIPN symptoms[53]. With the known benefits of exercise in chronic pain and cancer, combined with low risk of harm, supporting an increase in physical activity should be part of CIPN management[60; 108].

Mechanisms

By improving our understanding of the underlying mechanisms leading to the development and also factors contributing to chronicity, we can develop targeted treatments to reduce the significant impact that CIPN has on patients. The mechanism are complex, with peripheral, spinal and supraspinal changes, ranging from altered ion channel activity to changes in intracellular systems. A comprehensive analysis of these is beyond the scope of this review, and readers are referred to several recent reviews[15] [63].

It is, however, worth considering some of these mechanisms and how they might translate into clinical benefit. An overview is given in figure 3.

Ion channels—Sodium channels: In CIPN, as in some other types of neuropathic pain, alterations in sodium channel type and activity may contribute to the development of CIPN[27]. Expression of $Na_V1.7$ channel is increased in small fibre sensory neurones, in preclinical CIPN models, with increased spontaneous neuronal activity, with similar findings in human dorsal root ganglia in segments affected by CIPN[58]. An acute, Na channel mediated in neuronal excitability has been found in oxaliplatin treated patients who go on to develop chronic CIPN[77].

Potassium channels: Decreased potassium channel expression in primary sensory neurones has been found with several chemotherapy types, potentially leading to increased spontaneous neuronal firing[81; 112].

The combination of increased between Na channel and decreased K channel activity also predisposes towards hyper excitability, with agents that increase K channel hyperpolarization reducing CIPN features.[25; 72]

Calcium channels: Alterations in ion channel function and expressed subtypes have been widely described in neuropathic pain syndromes, including CIPN. Increase coupling of pre-synaptic calcium subunits (alpha-2 delta1) with the NMDA receptor has been shown in mice after paclitaxel, contributing to neuropathic pain features[22]. Type of chemotherapy may be important, with a decrease in Cav3.2 T type calcium channel was found with bortezomib, in mouse dorsal root ganglia[101]. However, in a rat model of paclitaxel neuropathy increased expression of Cav3.2 was found, associated with increase spontaneous activity in dorsal root ganglia neurones. Interestingly, this increased activity was found with infusion of lipopolysaccharide (an agonist at TLR4 receptors), and blocked by administration of a Cav3.2 inhibitor[59].

Transient Receptor Potential (TRP) channels: The TRP channels are known to be important in pain processing and thermal sensation, with demonstrated changes in neuropathic pain. Of these channels, the TRPVanilloid 1 (TRPV1) is activated by noxious heat, low pH, and by

exogenous capsaicin [84; 90]. It is found on c fibres and is upregulated in neuropathic pain conditions. Several rodent models of CIPN (rat and mouse) have shown increases in TRPV1 expression and activity, with evidence of thermal hyperalgesia[41; 80; 99]. Clinically, a high dose 8% capsaicin patch has been used topically for focal neuropathic pain: while there is limited high quality evidence for its use specifically in CIPN, there have been some reports of efficacy[16; 32]. The TRPM8 channel, activated by non-noxious cool temperatures, is upregulated on a subset of c fibres in neuropathic pain. Activation of the TRPM8 receptors by topical agents, such as icilin and menthol (in percentages less than 10%), results in analgesia in rodent models of neuropathic pain, with some early clinical evidence of efficacy for menthol in CIPN[31; 79].

Endocannabinoid systems—There are a number of models showing involvement of endocannabinoids in CIPN, with potential for analgesia through agents with activity at CB1 and/or CB2 receptors, which may be peripheral or central[71; 109]. Inhibition of endocannabinoid metabolism is an alternative approach, via inhibition of fatty acid amide hydrolase (FAAH) [10; 74]. There have been a number of early phase clinical trials investigating this class of drugs. Unfortunately, in a phase 1 study of a FAAH inhibitor (BIA 10-2474), there were serious adverse events, resulting in the death of one participant, and 5 other hospitalised with neurological issues[67]. This led to all clinical trials using FAAH inhibitors being stopped at that point. Subsequent evidence indicates that the SAEs were related to wider “off target” effects of BIA 10-2474, rather than a class effect of FAAH inhibitors, with clinical trials now resuming in this area[104]

Mitochondrial dysfunction—Mitochondria are small membrane bound intracellular organelles that provide cellular energy mainly via oxidative phosphorylation to produce adenosine triphosphate (ATP). Neuronal cells have high energy requirements, and as such, are sensitive to process that disrupt mitochondrial function, such as chemotherapeutic agents[76]. Different agents appear to have different mechanism by which mitochondrial dysfunction occurs. For example, platinum based compounds may affect protein synthesis within mitochondria, whereas taxanes impact on membrane depolarization with changes in calcium release[63]. As a result, there is an increase in oxidative stress within mitochondria and consequent continued dysfunction in neuronal energy production. Reduced maximal respiration capacity and mitochondrial basal respiration as well as reduced ATP production are all seen, with an increase in Reactive Oxygen Species (ROS) overwhelming endogenous anti-oxidant systems [9; 33; 34; 113]. Understanding these mechanisms and targeting them is one potential preventive strategy[63].

Non neuronal mechanisms—Inflammatory processes induced in central glial cell, and peripheral immune cells, contribute to CIPN development[63; 70]. A number of mechanisms are involved in these processes. Paclitaxel-induced microglial activation, with an increase in calcium/ calmodulin- dependent protein kinase II (CAMKII) stimulated overexpression of Brain Derived Neurotrophic Factor (BDNF), produced high levels of the pro-inflammatory cytokine,IL-6, and increased expression of NR2B glutamate receptor subunits. All these changes were reduced by administration of a CB2 receptor agonist [109]. Another study found that paclitaxel induced significant upregulation in IL-1α, IL-1β, IL-6, TNF-α, INF-γ

and MCP-1, which was attenuated by a TNF-alpha monoclonal antibody (etanercept) [1] In a vincristine CIPN model, the anti-inflammatory cytokine, IL-4, and associated STAT signalling was reduced, with an increase in pro-inflammatory cytokines such as IL-1-beta and TNF-alpha[92]. IL-10, an anti-inflammatory cytokine, may be important in recovery from CIPN, with preclinical evidence from both platinum and taxane-related CIPN [63].

Peripheral immune system cells such as macrophages and monocytes have been shown to be part of CIPN mechanisms. There may therefore be the potential for developing novel therapies with a unique mode of action, such as the chemokine CX3CL1 (fractalkine) and its receptor, expressed on monocytes, and important in communication with neuronal cells[70].

Matrix metalloproteinases (MMPs) are a class of enzymes involved in degradation of the extracellular matrix, with inhibitors showing some potential as anti-cancer agents [49]. An increase in MMP 2 and 9, with a decrease in the endogenous MMP inhibitor, TIMP1, was found in a paclitaxel mouse model, associated with the development of allodynia. If inhibited by intrathecal MMP9 monoclonal antibody, allodynia was reduced. In parallel, reductions in oxidative stress and inflammatory mediators were found in the dorsal root ganglia[102].

Central changes—There have been a few studies using neuroimaging in CIPN. There are clear changes in pain processing in response to a noxious stimulus compared to healthy volunteers, and to patients with cancer, but no CIPN. These altered responses are seen in areas of the brain involved in pain processing, such as the superior frontal gyrus, cingulate cortex and insula. Structural changes have also been seen with altered grey matter density[12; 73].

Discussion

In developing novel preventive or modifying treatment for CIPN, the complex interaction between cancer cells, immune system and neurons must be considered. In particular any novel therapies used during oncological treatment, must not interfere with the tumoricidal effects of chemotherapy. This creates an additional challenge compared to other types of neuropathic pain.

While there are some potential novel therapies to be explored for prevention and treatment of CIPN, there remains an urgent need to improve the efficiency of translation[93]. This will require true collaboration between clinicians, basic scientists and population health scientists. Lessons need to be learned from previous failures to translate promising compounds in preclinical models, and sometimes early phase clinical trials to clinical benefit. We need to consider how design of preclinical studies can be improved. As with clinical evidence, critical appraisal of the quality of preclinical studies, and risk of bias need to be considered. Issues such as proper sample size calculations, blinding and prospectively defined primary outcome measures should all be considered[3]. The relevance of the model to the clinical syndrome is also important, e.g. including behavioural assessment of spontaneous pain, studying male and female rodents[7; 69].

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Developing the use of neuroimaging and QST to better understand CIPN mechanisms in the clinical syndrome should also help increase successful translation, allowing direct study of pharmacodynamic effects, stratification of clinical trials by mechanisms, and identification of placebo responses. Whilst there are not yet clear clinical biomarkers that can be used to identify patients who are inherently more vulnerable to developing CIPN, or more likely to respond to a particular targeted treatment, using this approach, with detailed phenotyping (including validated patient self report questionnaires, psychophysical testing, genetic testing and neuroimaging) is a definite step towards this. Although not practical for routine clinical use, it may then be possible to move towards simple bedside tests as surrogate markers, directing individual treatment, and improving clinical trials for CIPN. A recent consensus meeting (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION)–Consortiium) has produced very useful recommendations about future trial design for CIPN, addressing many of these issues[37]. One area that needs to be explored further is whether or not sensitivity to chemotherapy is reflected in the efficacy of cancer treatment. If so, then it may be that more "personalised" chemotherapy regimens should be used, taking account of chemo sensitivity both in terms of efficacy and adverse effects, such as CIPN.

Summary

Using a strong translational approach to the problem of CIPN is most likely to be successful. Well-designed preclinical studies, reflecting the clinical situation as much as possible, combined with careful consideration of clinical trial design is needed. Working together to standardize assessment techniques and ensure that those used are robustly validated is important. Underlying CIPN mechanisms are wide ranging and therefore offer multiple targets for novel therapies. Whilst traditionally, pharmacological interventions have predominated, a holistic approach, with consideration of mechanistically driven non-pharmacological interventions is also needed. Collaboration will be the key to success, both between disciplines and countries – a challenge not to be underestimated, with many potential barriers and rewards.

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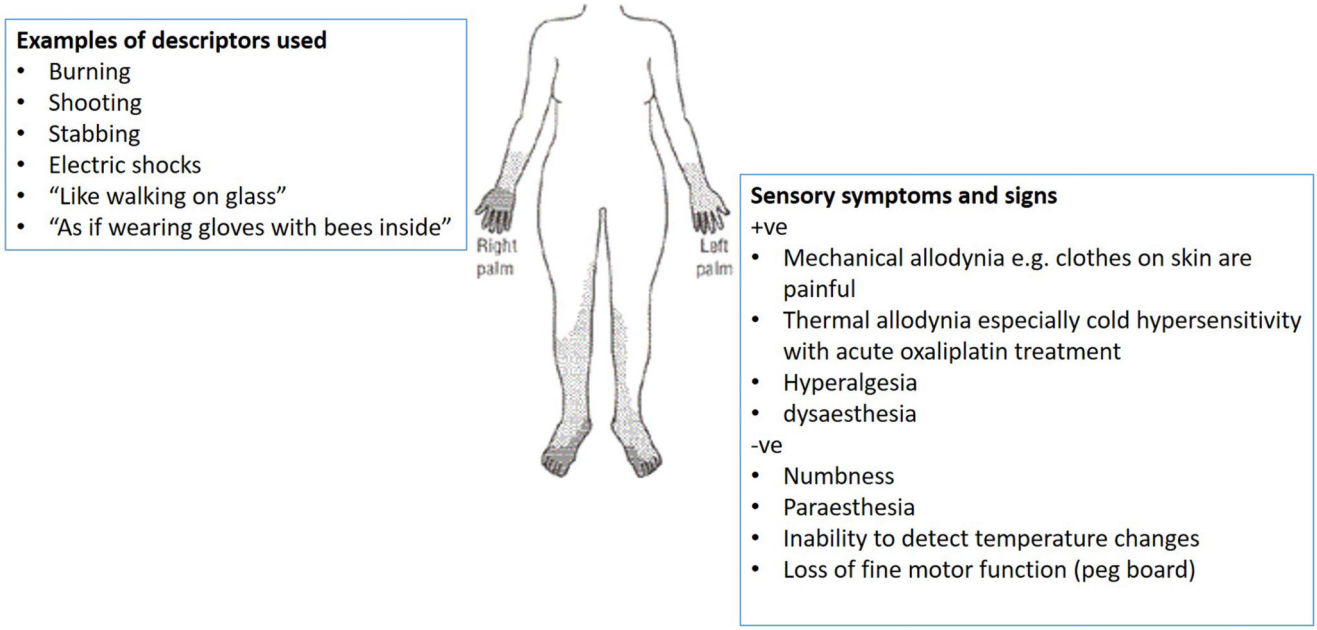

Figure 1.
Clinical features of CIPN.

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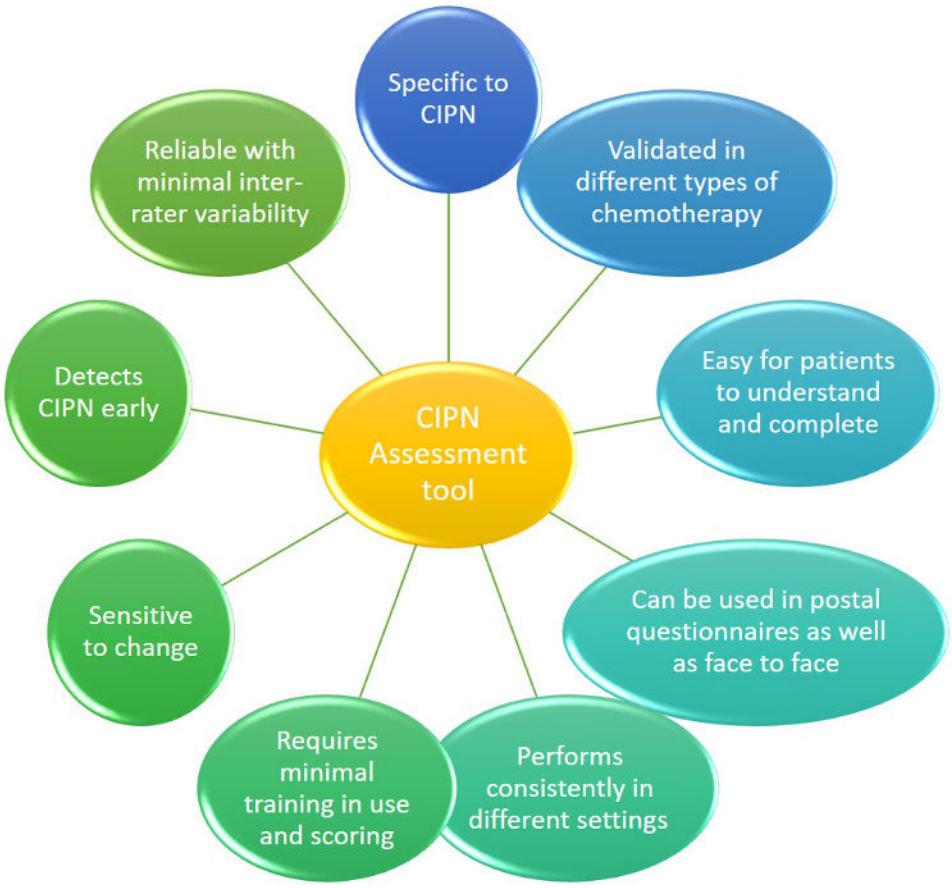

Figure 2.
Important components for an ideal CIPN assessment tool.

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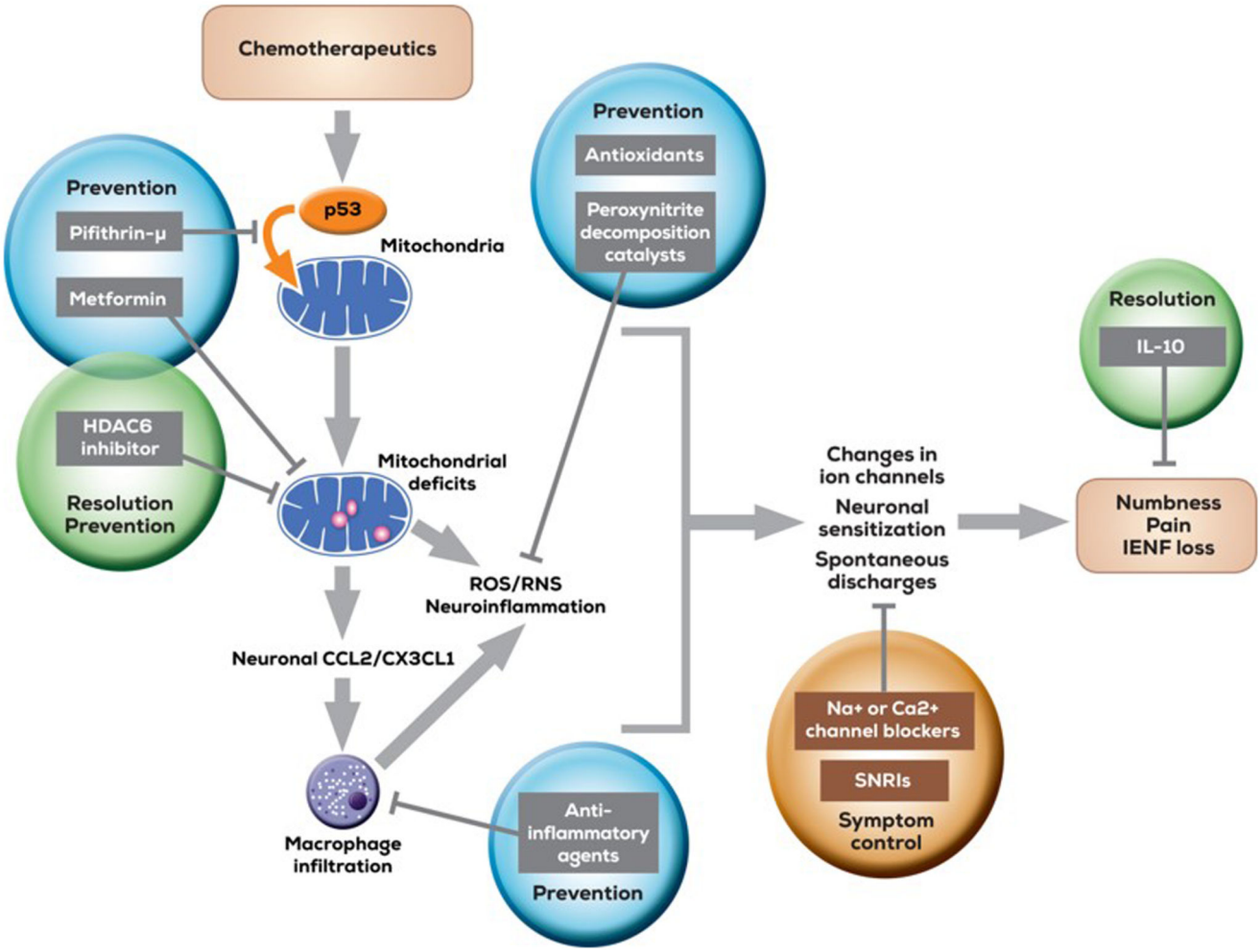

Figure 3.

Schematic overview of mechanisms underlying chemotherapy-induced peripheral neuropathy and mechanism-based disease interventions. CCL2 indicates C-C motif chemokine 2; CX3CL1, C-X3-C motif chemokine ligand 1; HDAC6, histone deacetylase 6; IL-10, interleukin 10; IENF, intraepidermal nerve fiber; RNS, reactive nitrogen species; ROS, reactive oxygen species; SNRIs, serotonin-norepinephrine reuptake inhibitors. From: Beyond symptomatic relief for chemotherapy-induced peripheral neuropathy: Targeting the source, Ma et al. Cancer, Volume: 124, Issue: 11, Pages: 2289-2298, First published: 20 February 2018, DOI: (10.1002/cncr.31248).

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Table 1

Common chemotherapeutics and incidence or prevalence of reported neuropathy.

Chemotherapy	Approximate incidence/ prevalence of CIPN (%)
Oxaliplatin	Acute: 85-96; Chronic wide range: 40-93
Cisplatin	12-85
Paclitaxel	61-92
Bortezomib	47
Vincristine	20
Combined cisplatin and paclitaxel	69-76

Supporting references: see[16; 24], [88]· Data is mainly from randomised controlled trials or prospective cohort studies.

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Table 2

Some of the risk factors associated with an increased risk of developing CIPN

Risk factor	Comments	Reference
Older age	May be due to lower chance of recovery from acute CIPN	[17; 78]
Medication: cardiovascular especially beta blockers	Opportunity to modify medication prior to starting chemotherapy.	[85]
Co-morbid health conditions	Those where there may be associated increased risk of neuropathy e.g. diabetes, HIV, excess alcohol, smoking; decreased creatinine clearance	[28; 88]
Raised Body Mass Index (BMI)	Potential mechanism not well understood, but may be related to pro-inflammatory state associated with obesity	
Low serum albumin	May reflect lower general health status	[40] [54; 82]
Use of opioids	Prolonged use more likely in patients with CIPN. Need further work to understand if this is due to pain severity, or to a mechanistic interaction with opioids increasing CIPN risk (OR 2.0, 1.06-3.69)	[91]

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Table 3

Some selected mechanisms by which chemotherapy may cause development and persistence of painful peripheral neuropathy

Potential mechanism of chemotherapy mitochondrial damage	Agent; action	References
Increased mitochondrial p53 (tumour suppressor molecule): Reduces mitochondrial membrane potential	Pifthrin-mu: prevents p53 accumulation in mitochondria without interfering with cancer killing effects of chemotherapy	[66] [57]
Disrupted axonal mitochondrial capacity via Histone diacetyl-6 (HDAC6) (deacetylates a range of substrates in the cytosol, such as tubulin and heat shock protein 90)	HDAC6 inhibitors: reverses/ prevents CIPN in preclinical models. Early stage clinical trials underway of safety in a variety of cancers, none focussing on CIPN (e.g.NCT02935790, NCT02632071, NCT02635061)	[56] [23; 86]
Reduced energy metabolism	Metformin: enhanced activation of carnitine palmitoyltransferase I, restoration of membrane potential; no clinical trials registered currently	[114] [43; 64; 75]
Increase in reactive oxygen species, overwhelming of endogenous mitochondrial anti-oxidant systems	Targeted mitochondrial anti-oxidants; accumulate in mitochondria and prevent CIPN related damage	[6; 36; 68]
Reduced mitochondrial respiration and energy production	Mitochondrial targeted peptide (SS 20): promotes mitochondrial respiration and positive effect on energy producing mechanisms	[103]