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Chemotherapy-Induced Peripheral Neuropathy

Natural therapies

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is characterized by a variety of symptoms including paresthesia, numbness, burning pain, allodynia and hyperalgesia, typically in a "stocking and glove" distribution. It affects a large percentage of chemotherapy recipients often leading to delay or cessation of treatment, which can be detrimental to their cancer recovery. Sadly, patients are often left with the symptoms of this debilitating condition long after treatment has stopped. Little is understood of CIPN, despite the research that has been conducted into pharmaceutical and natural therapies. Currently there is no consistent standard of care to manage this condition. This review serves to highlight the current state of evidence regarding the theorized pathophysiology of CIPN, the chemotherapeutic agents most responsible, the pharmaceutical agents commonly used to manage it, and the natural therapies offering new hope to reduce neurological symptoms in this patient population.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a severe, dose-limiting toxicity condition causing a variety of sensorimotor deficits including paresthesia, numbness, burning pain, allodynia and hyperalgesia, typically appearing in a "stocking and glove" distribution (Areti 2014, Han 2013). CIPN is most often a sensory neuropathy as described, but motor neuropathy is also possible. This may manifest as weakness of distal muscles or reduced deep tendon reflexes (Bristol-Myers Squibb 2011, GlaxoSmithKline 2002, Sanofi-aventis 2010). It is experienced by 30-40% of chemotherapy patients on average with reports of up to 70% depending on the chemotherapeutic agent used (Areti 2014, Beijers 2012). Often, the experience of CIPN does not resolve after treatment has stopped (Han 2013). Its pervasiveness amongst chemotherapy patients has led the National Cancer Institute to deem it a major cause of treatment cessation. Therein lies the potential for decreased chemotherapeutic efficacy and higher relapses of cancer (Areti 2014).

A variety of chemotherapeutic agents are associated with CIPN: platinum compounds (cisplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine), epothilones (ixabepilone), proteasome inhibitors (bortezomib) and thalidomide. While the exact mechanisms of nerve damage are not completely clear, theories abound including: microtubule disruption, oxidative stress and subsequent mitochondrial damage, altered ion channel activity, myelin sheath damage, DNA damage and neuro-inflammation (Areti 2014). Nerves have a higher amount of phospholipids, mitochondria-rich axoplasms and weak cellular oxidative defenses making them more susceptible to damage. Furthermore, anti-cancer drugs cause free-radical production leading to greater physical neuron damage by demyelination, mitochondrial dysfunction, microtubular damage and apoptosis. Overall, oxidative stress seems to be the biggest issue. This is also known to be a factor in Charcot-Marie-Tooth disease and diabetic neuropathy – two of the most common neuropathic disorders (Areti 2014). Oxidative damage is compounded by a number of other factors: polychemotherapy in cancer treatment (Areti 2014), use of other non-chemotherapeutic drugs, patient age, preexisting conditions such as pernicious anemia, diabetes, HIV/AIDs, alcoholism, and/or vitamin B12 deficiency (Armstrong 2005).

With such diverse effects on the nerves, a number of strategies have been investigated for prevention and treatment of CIPN. There are few clear winners amongst the pack, and there is currently no widely-accepted primary prevention or treatment regimen for CIPN (Hershman 2014). This paper will review current practice with respect to pharmaceutical interventions and discuss the evidence on naturopathic nutraceutical and acupuncture strategies for prevention and treatment of CIPN.

Allopathic Treatment Options

There are many publications exploring allopathic management of CIPN. Medical researchers have reached into their toolboxes to determine if well-known symptomatic treatments for non-chemotherapy-induced neuropathic conditions (e.g. diabetic neuropathy) will benefit those suffering from CIPN. These include NSAIDS, opioids (oxycodone and tramadol), gabapentin, recombinant human leukemia inhibitory factor, SSNRIs (venlafaxine, duloxetine), tricyclic antidepressants (TCAs) (nortriptylline and amitriptylline), anticonvulsants (carbamazepine, pregabalin, lamotrigine), and erythropoietin. Unfortunately, all of these allopathic therapies are utilized in an attempt to control the unpleasant symptoms of neuropathy rather than preventing or actually treating it. Such symptomatic therapies are not specific to the underlying cause of the neuropathy and often provide little to no effect when formally studied in clinical trials (Kaley 2009).

Overall, allopathic treatment of CIPN has proven to be wrought with difficulties. As such, there is great interest in a naturopathic approach to CIPN management.

Naturopathic Treatment

There are a number of naturopathic therapies that have been investigated for management of CIPN. These include both nutraceuticals and acupuncture. A notable difference with the naturopathic approach to neuropathy is that various natural agents have actual neuroprotective and neuroregnerative potential. This is a large improvement over a purely conventional approach, which only masks neuropathic pain. When used for CIPN prevention, nutraceuticals must also show that they are able to reduce the neurotoxic effects of the chemotherapeutic agents, while not interfering with its anti-tumour activity. Well-accepted nutraceutical options include calcium and magnesium infusions with multiple studies also focused on acetyl-L-carnitine (ALC). Acupuncture is also an up-and-coming field of research for CIPN management, especially because it can be used in conjunction with chemotherapy without risk of interaction. This review will cover evidence pertaining to a range of natural therapies including ALC, N-acetyl-cysteine (NAC), glutathione, alpha-lipoic acid (ALA), vitamins B6, B12 & E, calcium, magnesium, glutamine, omega-3 fatty acids, melatonin and acupuncture will be reviewed.

Acetyl-L-carnitine

The mechanism of action of ALC is unclear. It is theorized that ALC may modulate nerve growth factor expression and promote nerve regeneration to increase nerve conduction and velocity (Kaley 2009), while also blocking A-fiber and C-fiber nociceptor firing (Bianchi 2005). It acts as an antioxidant to move acetyl groups across mitochondrial membranes, while also playing a role in catabolic and anabolic

mechanisms (Pachman 2011). Pisano (2003) investigated the potential role of ALC in the treatment of paclitaxel- and cisplatin-induced peripheral neuropathy in rat models revealing a significant difference in CIPN with no effect on anti-tumour activity. However, a recent phase III trial failed to show significant prevention of CIPN when ALC was administered concurrently with taxane chemotherapy (Hershman 2012). That being said, it has still shown benefit in the treatment of CIPN post-chemotherapy with cisplatin and paclitaxel (Areti 2014, Bianchi 2005, Maestri 2005, Schloss 2014). While it is highly tolerable, nausea and insomnia have occasionally been reported with its use (Bianchi 2005, Maestri 2005). Patients with a history of seizures must use ALC cautiously, since it can increase seizure frequency (De Grandis 1995, Hendler 2001, Juvenon Inc 2003, Zdanowicz 2001).

N-acetyl-cysteine (NAC)

NAC acts to increase glutathione concentration, while decreasing the cytotoxic effects of platinum adducts in the dorsal root ganglia (Kaley 2009, Schloss 2013). In a recent randomized pilot study conducted by Lin (2006), fourteen stage-three colon cancer patients receiving oxaliplatin were treated with oral NAC. Fewer patients in the treatment group developed CIPN, however, the small sample size meant the results did not reach statistical significance. It would be beneficial to conduct a larger study of this potentially effective preventative agent.

Glutathione

Glutathione supplementation has shown good effect in treating CIPN patients (Pachman 2011, Piccolo 2014). It has a high affinity for heavy metals, thereby reducing platinum adducts causing oxidative damage in the dorsal root ganglia (Piccolo 2014). A number of clinical trials have also reported that glutathione does not affect chemotherapeutic activity while reducing neurotoxic effects, especially when treating oxaliplatin-induced peripheral neuropathy (Cascinu 2002, Cascinu 1995). An RCT conducted in 52 patients with colorectal cancer treated with oxaliplatin with or without the addition of glutathione reported significantly reduced incidence of grade two to four neuropathy based on National Cancer Institute common toxicity criteria (p=0.003) assessed after 12 cycles of chemotherapy, as well as better sensory nerve condition on electrophysiological testing associated with glutathione treatment (Cascinu 2002). The chemotherapy response rate was 26.9% in the glutathione arm and 23.1% in the placebo arm, indicating no reduction in the effectiveness of oxaliplatin (Cascinu 2002).

Glutathione has also been investigated with cisplatin therapy. There is a phase II trial suggesting lack of negative interaction between glutathione and cisplatin in patients with ovarian cancer when glutathione was given at 2500mg IV before cisplatin infusion (Locatelli 1993). Another early prospective study assessed administration of IV glutathione prior to cisplatin infusion in ovarian cancer patients, and while there was no comparator group, authors judged that "use of GSH is a safe new method for high-dose cisplatin administration. This regimen is well-tolerated and very effective in ovarian cancer patients with bulky disease and warrants further evaluation" (Di Re 1990). Finally, an RCT conducted in patients with ovarian cancer demonstrated that use of glutathione led to decreased toxicity, resulting in a significantly greater percentage of patients able to receive treatment with six rounds of cisplatin compared with patients not co-treated with glutathione, 58% versus 39%, (p = 0.04) (Smyth 1997). Importantly, the group treated with glutathione plus cisplatin demonstrated a non-significant trend to better treatment response as assessed clinically, 73% versus 62% (p=0.25).

A 2014 Cochrane review assessing the role of agents including glutathione for the prevention of neuropathy induced by platinum drugs concluded that there is insufficient evidence to conclude efficacy in preventing CIPN, but noted "modest but promising (borderline statistically significant) results favouring [its] ability to reduce the neurotoxicity of cisplatin and related chemotherapies" (Albers 2014).

Alpha-Lipoic Acid (ALA)

Gedlicka (2003) has investigated ALA use in CIPN patients caused by docetaxel/cisplatin showing beneficial results with no side effects. ALA is a potent lipophilic antioxidant that is suspected to decrease oxidative stress (Gedlicka 2003, Pachman 2011). It also has proven benefits in the treatment of diabetic neuropathy (Bertolotto 2012). Guo et al (2014) studied 243 cancer patients in a randomized, double-blind placebo-controlled trial where ALA (or placebo) was dosed orally at 600mg three times daily. Only 70 patients completed the trial due to compliance issues. As such, clinical significance could not be determined. The authors suggest that intravenous therapy may allow for greater patient compliance, and more studies are needed to properly investigate ALA.

Vitamins B6 and B12

Diagnostic evaluation of CIPN often involves testing vitamin B6 and B12 levels, since deficiencies of these agents are known to cause peripheral neuropathy. An early double-blind, randomized, placebo-controlled trial found vitamin B6 significantly reduced CIPN from cisplatin and hexamethylmelamin administration (Wiernik 1992). This study also observed a reduced response duration associated with B6 use, however, with a median of 6.4 months until progression in the B6 group, compared to 10.1 months it the group without B6 treatment (Wiernik 1992). However, there was no impact from use of B6 on time to treatment failure or overall survival (Wiernik 1992). Other studies of B6 suggest an opposite effect, protecting against capecitabine (5-fluorouracil prodrug, Xeloda) induced hand-foot syndrome, but showing no deleterious effect on anti-tumour effects (Corrie 2012). In this study, administration of pyridoxine resulted in "an increased rate of avoiding capecitabine dose modifications (37% vs 23%, relative risk 0.59, 95% CI 0.29, 1.20, P=0.15) and fewer grade 3/4 HFS-related adverse events (9% vs 17%, odds ratio 0.51, 95% CI 0.15-1.6, P=0.26)" (Corrie 1992). Further research is needed to better elucidate the effects of B6 on specific chemotherapy regimens.

Vitamins B6 and B12 have also been well-evaluated in diabetic neuropathy since they are key cofactors for a number of metabolic processes including DNA synthesis and regulation (Miranda-Massari 2011, Xu 2013), which increases the biological plausibility that they may prove useful in CIPN as well.

Calcium and Magnesium

Calcium and magnesium infusions have been shown to be especially beneficial for oxaliplatin-induced peripheral neuropathy. Oxalate (a metabolite of oxaliplatin) is toxic to voltage-gated sodium channels, and chelation of oxalate with calcium and magnesium appears to prevent neuropathy (Kaley 2009, Pachman 2011). While trials to date have investigated small sample sizes and have produced limited data, the evidence is supportive in general (Gamelin 2004, Grothey 2011). Gamelin demonstrated benefit on neuropathy without affecting tumor response rate: 20% of patients in the treatment group developed neuropathy compared to 45% in the control group (2004). In the Combined Oxaliplatin Neurotoxicity Prevention Trial (CONCEPT), Grothey showed that calcium magnesium infusion reduced grade two or greater sensory neuropathy as well as oxaliplatin induced sensory neuropathy in patients with colorectal cancer on infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) (2011). Interim results of this study reported possible decreased response rates associated with calcium magnesium therapy, however upon analysis of the final data, a null effect on response rates was found (Grothey 2011).

Finally, a retrospective analysis of 755 patients with colorectal cancer found that the incidence of all grade neurotoxicity in the Ca/Mg(+) group and the Ca/Mg(-) group was 85% and 92%, respectively ($p = 0.02$), and the response rate was 43.1% versus 50%, respectively ($p = 0.11$), respectively, indicating benefit on incidence of neuropathy without reduction in anticancer effects (Knijn 2011). Calcium gluconate and magnesium sulfate have been proposed to increase the concentration of extracellular calcium and decrease the hyperexcitability of neurons exposed to oxaliplatin (Wolf 2008).

Glutamine

Glutamine is a non-essential amino acid stored in skeletal muscle and the liver, which can decline during long periods of stress, such as malignancy (Beijers 2012). Glutamine is known to up-regulate nerve growth factors in animal models (Gwag 1997, Vandat 2001, Wolf 2008) and is thought to be best used as a neuroprotective agent (Stubblefield 2005, Vahdat 2001, Visovsky 2007). Wang (2007) initially reported a study using glutamine for prevention of oxaliplatin-induced neuropathy that showed a significantly lower incidence of neuropathy in the glutamine group after four cycles. However, other studies have not shown clinical significance (Vahdat 2001). Glutamine may have a role in neuroprotection, but data from larger, double-blinded, randomized, placebo-controlled trials is still needed.

Omega-3 Fatty Acids

Omega-3 fatty acids (eicosapentanoic acid, EPA and docosahexanoic acid, DHA) are polyunsaturated fats, integrated into the phospholipid membrane of peripheral nerves. They help to regulate signal transduction, while also inhibiting pro-inflammatory cytokines causing neuropathy, and reducing the production of further pro-inflammatory mediators (Coste 2003, Shapiro 2003). Researchers believe omega-3 fatty acids require further studies using larger sample sizes, but current results show promise for both CIPN prophylaxis and treatment (Areti 2014, Schloss 2013).

A couple of recent RCTs show benefit from omega-3 fatty acids on CIPN. Ghoreishi et al found that treatment with approximately 1800mg combined EPA+DHA (10% EPA component) significantly reduced the incidence of paclitaxel-induced peripheral neuropathy in breast cancer patients (2012). The number of patients not developing neuropathy was 21 (70%) in the omega-3 fatty acid group, compared to 11 (40.7%) in the placebo group,odds ratio OR = 0.3, .95% CI 0.10-0.88, $p = 0.029$). Another RCT in patients with non small cell lung cancer (NSCLC) on paclitaxel and cisplatin/carboplatin treatment found that supplementation with an EPA-enriched supplement (100% EPA component) resulted in improvements in several parameters including fatigue, appetite, and neuropathy: while the control group had significant increases in nausea and vomiting ($p=0.02$) and neuropathy ($p=0.004$) associated with chemotherapy, the EPA-treated group showed no change ($p>0.05$) (Sánchez-Lara 2014).

Importantly, omega-3 fatty acids have

not only been shown to not interfere with the effectiveness of chemotherapy, but in select patient populations they may even improve anticancer effectiveness, adding further benefit to their use in these situations. Notably, in patients with non-small cell lung cancer undergoing first-line treatment with carboplatin with vinorelbine or gemcitabine, use of 2.5g omega-3s containing 2.2g EPA + 240-500mg DHA resulted in significantly higher response rates (60.0% vs 25.8%, p = .008) and a trend toward longer overall survival (60.0% vs 38.7%; p = .15) (Murphy 2011).

Melatonin

Melatonin is a pineal hormone that naturally enhances neuroprotection by inhibiting the production of free radicals. Research conducted by Nahleh showed the connection between taxane-induced peripheral neuropathy and concurrent oral supplementation with melatonin (2010). Twenty-two breast cancer patients were dosed 21mg of melatonin at bedtime daily for 28 days. Results revealed a reduction in CIPN symptoms whereby 45% of patients experienced only mild neuropathy and 55% of patients experienced no neuropathy at all. Furthermore, there was no reduction of chemotherapeutic effect. Technically, the results are not considered statistically significant due to the sample size of 22 patients. Since positive results were elucidated by this trial, and since melatonin has been useful in treating other cancer symptoms including cachexia, stomatitis, and asthenia, it would be ideal to further investigate melatonin's effect on CIPN with larger clinical trials. Furthermore, two meta analysis of RCTs investigating melatonin in combination with chemotherapy have shown lack of negative interactions on anticancer effects, with improved survival at one year, and a reduction of other side effects of chemotherapy, respectively (Mills 2005, Seely 2012).

Vitamin E

According to Areti, the evidence supporting vitamin E is controversial (2014). While a large trial conducted by Kottschade showed no significant difference in patients treated with all varieties of CIPN (2011), smaller studies by Pace (2003) and Argyriou (2012) found a significant benefit. Vitamin E is useful for protection against microtubule dysfunction caused especially by cisplatin. Larger studies are needed to show proof of efficacy (Kaley 2009, Pachman 2011, Piccolo 2014, Schloss 2013).

Capsaicin

There are currently no clinical trials studying the use of capsaicin in CIPN specifically, but other neuropathic conditions show benefit from treatment with capsaicin due to its depletion of substance P in distal nerve endings (Kaley 2009). Topical symptom control strategies offer benefit over oral medications simply because they have reduced absorption and therefore less risk of systemic toxicity and interference with chemotherapeutic agents (Pachman 2011).

Acupuncture

While its physiological mechanism is not fully understood, acupuncture has been studied for its energetic ability to ease the symptoms of CIPN. Acupuncture has been previously studied for peripheral neuropathy experienced in HIV and diabetic patients with positive results (Abuaisha 1998, Phillips 2004). Wong conducted a pilot prospective case series of 5 patients, which treated Traditional Chinese Medicine elements of Qi and Blood (2006). It revealed a reduction in CIPN across all patients while maintaining remission. A later trial conducted by Schroeder provided similar results suggesting larger, randomized trials are needed, especially since acupuncture has no known interaction with chemotherapy drugs (2012).

Recommendations

While there is an abundance of natural therapies with a theoretical basis for managing CIPN, there are a number of limitations that affect their study. Each chemotherapeutic agent has a different effect on neurons, as does each natural therapy, meaning it is difficult to find a single comprehensive treatment for CIPN. Furthermore, appropriate measures for assessing CIPN severity are as varied as the symptoms themselves, resulting in difficulty in comparing the results of different studies. Finally, while many studies have been conducted in total, the research base on individual agents and use of adequate sample size to produce definitive results is sometimes lacking as a result of limited available funding for research on non-proprietary agents.

Another serious limitation of the current body of literature is lack of trials examining the role of combination naturopathic therapy. Due to the multiple mechanisms of nerve injury induced by chemotherapy, it would be reasonable to theorize that a combination of natural medications with a diverse range of neuroregnerative properties may be more efficacious than single agent therapy. For example, in the authors' experience, a combination of high doses of B vitamins with high dose ALA and ALC can have a profound and lasting effect on debilitating, intractable CIPN (post-chemotherapy), with minimal side effects. Where possible, use of the activated forms of vitamins is recommended, for example methylcobalamin (B12), pyridoxal-5-phosphate (P5P, B6) and benfotiamine (B1), in order to circumvent any factors notably genetic polymorphisms that may impede adequate in vivo conversion by individuals.

With respect to individual nutraceuticals, current studies demonstrate limited evidence for their administration in conjunction with chemotherapeutic agents. The most well-established CIPN therapies include:

- oral vitamin E with cisplatin (Argyriou 2012, Pace 2003)
- oral vitamin B6 with cisplatin (Corrie 2012, Wiernik 1992)
- omega-3 fatty acids with paclitaxel (Ghoreishi 2012, Sánchez-Lara 2014)
- intravenous glutathione with oxaliplatin (Cascinu 2002, Cascinu 1995)
- intravenous calcium magnesium with oxaloplatin (Gamelin 2004, Grothey 2011)

Further research is needed before these nutraceuticals are established as routine CIPN prophylactics. Therapies like melatonin, calcium and magnesium injections, glutathione and ALA deserve larger investigations. Finally, acupuncture

should also be considered for larger scale trials since it is well-tolerated and effective without interfering with the efficacy of chemotherapeutic agents.

Since CIPN is a severe side effect of neurotoxic chemotherapy, treatments aimed at prevention, treatment or alleviating the symptoms are in high demand. Naturopathic treatments with neuroprotective and neuroregenerative potential have a particularly important role in this area. With continued research it is likely that natural therapies will come to the forefront as leading treatments for this crippling condition. ■

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