Online International Breast Cancer Rehabilitation Summit 2016
Presenter: Janet Schloss

Topic: Review on current potential prevention and management options for chemotherapy-induced peripheral neuropathy (CIPN)

Background

Neurological complications such as chemotherapy-induced peripheral neuropathy (CIPN) and neuropathic pain are frequent side effects of neurotoxic chemotherapy agents

An increased survival rate and frequent administration of adjuvant chemotherapy regimens involving neurotoxic agents makes it imperative that accurate diagnosis, prevention and treatment of these neurological complications be addressed.

Currently, the main treatment is dose reduction or cessation of treatment with that chemotherapy agent

It is estimated that a third of all patients who undergo chemotherapy experience CIPN. [1]

Patients experiencing moderate to severe CIPN report:

–*reduced quality of life* [2]

–*chronic discomfort* [3]

–*disruption of physical abilities for general life activities which can be temporary or permanent.* [2]

Mechanism of action for CIPN

■Each neurotoxic agent has its own mechanism of action

■Administration of chemotherapeutic agents results in numerous cellular changes

–Loss of sensory terminals in skin

–Alterations of membrane receptors

–Changes in intracellular signalling, neurotransmission and excitability

–Changes in cellular metabolism

■ These changes negatively influence neuronal and glial cell phenotypes leading to CIPN development

Discussion on Mechanism of Action for CIPN

■New genetic testing may provide a new avenue for clinicians to identify patients at high risk of developing CIPN

■Retigabine (a voltage-gated potassium channel opener) offers the greatest potential for protection and treatment options

■Voltage-gated calcium drugs such as gabapentin and ethosuximide may decrease reflex hypersensitivity

■Down regulating glutamate transporters may have potential protective effects e.g Acetylcholinesterase inhibitors (Alzheimer's medication such as donepezil

■Menthol cream has shown promise

■Stimulating NGF may assist e.g. vitamin B12, acetyl-L-carnitine, N-acetyl cysteine, rosemary, Polygala tenuifuloa, Codonopsis pilosula, and Dioscorea nipponica.

■Minocycline may prevent CIPN from oxaliplatin and paclitaxel

■Reducing inflammation could provide protection against CIPN. CM that has been trialled for CIPN with some benefit which have anti-inflammatory action include:

–Omega 3 fatty acids,

–Vitamin E,

–Curcumin, chamomile,

–Sweet bee venom,

–Certain Asian herbal medicines

Pharmaceutical Agents for CIPN

Chemotherapy agent	Pharmaceutical agents trialed	Level of evidence	Total No	Recommendations
Cisplatin	Amifostine[58-64]	Level III	657	Possible ototoxicity protection particularly for children Limited protection for CIPN
Oxaliplatin	Amifostine[65]	Level IIIc	15	Possible decrease in severity of CIPN by subcutaneous application
	Carbomazepine/ oxcarbazepine[66-69]	Level IIIb	103	Limited protection noted
	Calcium channel blockers[70]	Level IIIb	116	Retrospective study found they lowered the incidence for acute CIPN but not chronic
Taxanes	Amifostine[61,71,72]	Level III	98	Possible protection against severe CIPN development
Vincristine	Amifostine[64]	Level IIIa	97	No protection noted
Carboplatin/ taxane	Amifostine[73-77]	Level III	446	Possible protection against severe CIPN development
	rhuLIF[78]	Level II	117	No protection noted

Chemotherapy agent	Pharmaceutical agents trialed	Level of evidence	Total No	Recommendations
CIPN treatment	Gabapentin[79,80]	Level II	177	Failed to show any benefit although may decrease pain in some people
	Lamotrigine[81]	Level II	131	No benefit noted
	Pregabalin[57]	Level IIIb	23	May decrease the severity of sensory oxaliplatin PN in patients who reach the target dose of 150 mg tds (22%)
	Amitriptyline/nortriptyline[82,83]	Level III	95	Modest effect on reducing pain
	Venlafaxine[54-56]	Level IV	4	Possible effect on reducing pain although only case studies
	Duloxetine[52,53]	Level II	232	Statistically significant in reducing pain from CIPN

Nutraceuticals trialled for CIPN

Chemotherapy agent	Nutraceutical trialed	Level of evidence	Total no	Recommendations
Cisplatin	Vitamin E[84,86 ,93]	Level II	190	Recommended as an adjunct during treatment to prevent CIPN. Dose 400 mg/day
	Glutamine[94]	Level III	26	Possible recommendation as it may reduce severity of CIPN. Dose: 2 days consequently with cisplatin
	Alpha-Lipoic acid[95]	Level II, Level IIIa	243	Not recommended as no protection noted
	Glutathione[96-98]	Level II	244	Trend toward protection. Dose: 1.5–2.5 g daily
	Vitamin B6[89]	Level IIIb	248	Prevented CIPN but adversely affected response duration. Dose: 300 mg daily
Oxaliplatin	Magnesium/ calcium infusions[94,99-104]	Level II	418	Conflicting results but is not recommended to use in conjunction with treatment
	Vitamin E[105]	Level II	34	Not recommended as no differences noted. Dose: 400 mg/day
	Alpha-lipoic acid[96,106]	Level III	15	Reduced severity of severe CIPN. Dose: 800 mg daily
	N-acetyl cysteine[107]	Level IIIa	14	Not recommended as no differences noted. Dose: 1200 mg daily
	Glutathione[87,89]	Level II, Level IIIb	79	Possible protection as one trial had a significant protective effect. Dose: 1500 mg
	Glutamine[108]	Level IIIa	88	Possible recommendation as it may reduce severity of CIPN. Dose: 15 g twice a day, or IV 20 g for 2 days consequently with oxaliplatin
	Vitamin B6[109]	Level II	23	Recommended, as it may prevent CIPN

Taxanes	Glutamine [150, 151]	Level IIIa	47	Not recommended as it was not statisically signficant Dose: 10g t.i.d for 4 days after chemotherapy
	Acetyl L Carnitine [152]	Level IIIa	409	Not recommended as worsened CIPN in patients taking ALC. Dose: 3,000mg daily
	Omega 3 Fatty acids [55]	Level IIIa	69	Recommended as it showed statistical signficance. Dose: 640 mg t.i.d
	Vitamin B12 [153]	Level IIIb	1	Recommended as possible protection. A case study from a trial of 71 people. Dose: 1000mcg daily

Chemotherapy agent	Nutraceutical trialed	Level of evidence	Total no	Recommendations
Cisplatin/taxol	Vitamin E[99.114]	Level II	247	Not recommended but may have possible protection in some patients. Dose: 400 mg/day
Bortezomib	Acetyl-L-carnitine[115]	Level II	19	Not recommended to be given prophylactically
CIPN treatment	Acetyl-L-carnitine[92. 93]	Level IV	51	May provide improvement of symptoms if administered after chemotherapy cessation. Dose: 1 g t.i.d
	Alpha-lipoic acid[116]	Level III	14	Improved neurological symptoms. Dose 600 mg IV weekly over 3–5 weeks

Herbal medicines trialled for cipn

Chemotherapy agent	Herbal medicine trialed	Level of evidence	Total no	Recommendations
Oxaliplatin	Ginkgo biloba[117]	Level IIIb	17	Possible neuroprotection, do not use with patients who are on blood thinning medication including aspirn or on avastin/eribitux
	Buyang huanwu[118]	Level II	84	Decreased CIPN but information not given. This is a tea that could be drunk through chemotherapy
	Geranii herba plus Aconiti radix[119]	Level II	58	Was found to decrease neuropathic pain but information not given
	Gosha-jinki-gan (GJG) [120,121,122,123]	Level II	238	Recommended as it had a positive response. Found to have neuroprotective values. However, only available in Japan and certain Asian countries
	Kieshikajutsubuto[124]	Level III	11	Patients had 76.6% improvement. Recommended
	Ogikeishigomotsuto[125]	Level IIIb	1	Decreased neuropathic pain but only a case study. Further research needed
	Shakuyaku-kanzo-to[126]	Level IV	44	50% responded to this while 65% responded to GJG. Both can be recommended in Asian countries
Paciltaxel	Modified Chai Hu Long Gu Mu Li Wan[127]	Level IIIa	48	Possible neuroprotection. Worth considering
	Gosha-jinki-gan (GJG)[128]	Level IIIa	82	Possible neuroprotection and better when administered early. Recommended
	Shakuyaku-kanzo-to[129]	Level III	23	Reduced neuropathic pain. Worth trying as a treatment option
Taxol/carboplatin	Sweet bee venom[130,131]	Level IV	16	This is a treatment for CIPN and involves injecting into the acupuncture point. Was found to decrease pain and neuropathy. Requires a qualified and skilled practitioner to administer for treatment

Other therapies trialled for cipn

■Acupuncture has shown promise as a treatment option for CIPN

■Topical application of analgesic options:

–Combination of baclofen 10mg, amitriptyline HCL 40mg (3%), and ketamine 20mg (1.5%) in a base of pluronic lecithin organogel was found to be beneficial (p=0.053)

–Menthol (1%) found to be beneficial for neuropathic pain with CIPN

–Capsicum cream (e.g. Zostrix) found to be beneficial for neuropathic pain

–???? Trials looking at topical application of cannabis oil in creams for neuropathic pain with CIPN still be completed

Discussion

■The new insights into the mechanisms of action of CIPN may assist complementary medicine researchers to identify potential nutrients or herbs that could assist in the prevention or treatment of CIPN

■Currently there is no standard prevention or treatment options.

■Isolating specific nutrients or herbal medicine for each neurotoxic chemotherapy agent has great potential due to the lower side effect profile

Conclussion

■Clinicians and researchers acknowledge that there are numerous challenges involved with understanding, preventing and treating CIPN

■Currently, the preferred treatment is still dose reduction or cessation

■Possible pharmaceutical treatment options include duloxetine or pregabalin.

■Possible nutraceuticals for prevention include:

–Vitamin E for cisplatin

–Omega 3 fatty acids (fish oils) for taxanes

–Lipoic acid for oxaliplatin

■Possible nutraceutical treatment options include acetyl-L-carnitine

■Possible herbal medicine prevention option for oxaliplatin is Gosha-jinki-gan from Japan

■Acupuncture and topical creams may assist with neuropathic pain

Thank you for your time

Dr Janet Schloss
Office of Research, Endeavour College
Email: janet.Schloss@endeavour.edu.au