Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose limiting side effect of many commonly used chemotherapeutic agents, including platinum drugs, taxanes, epothilones and vinca alkaloids, and also newer agents such as bortezomib and lenolidamide. Symptom control studies have been conducted looking at ways to prevent or alleviate established CIPN. This manuscript provides a review of studies directed at both of these areas. New evidence strongly suggests that intravenous calcium and magnesium therapy can attenuate the development of oxaliplatin-induced CIPN, without reducing treatment response. Accumulating data suggest that vitamin E may also attenuate the development of CIPN, but more data regarding its efficacy and safety should be obtained prior to its general use in patients. Other agents that look promising in preliminary studies, but need substantiation, include glutamine, glutathione, N-acetylcysteine, oxcarbazepine, and xaliproden. Effective treatment of established CIPN, however, has yet to be found. Lastly, paclitaxel causes a unique acute pain syndrome which has been hypothesised to be caused by neurologic injury. No drugs, to date, have been proven to prevent this toxicity.

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose limiting side effect of many older commonly used chemotherapeutic agents, including platinum drugs, taxanes, epothilones and vinca alkaloids, but also newer agents such as bortezomib and lenolidamide (Table 1).1,2 The incidence of CIPN can be variable, but often ranges from 30 to 40% of patients receiving chemotherapy. A number of factors influence the incidence of CIPN in patients receiving neurotoxic chemotherapy, including patient age, dose intensity, cumulative dose, therapy duration, coadministration of other neurotoxic chemotherapy agents, and pre-existing conditions such as diabetes and alcohol abuse. While symptoms may resolve completely, in some instances CIPN is only partly reversible, and in other cases it does not appear to be reversible at all.1,3 CIPN can be extremely painful and/or disabling, causing significant loss of functional abilities and decreasing quality of life. Neurotoxic chemotherapeutic agents may cause structural damage to peripheral nerves resulting in aberrant somatosensory processing of the peripheral and/or central nervous system.4 This resultant peripheral neuropathy can potentially affect both small fibre axons (temperature, pin prick) and large fibre sensory axons (vibration, proprioception). A common clinical course begins with paraesthesias (tingling) and dyasaesthesias, commonly located in the toes and fingers. These symptoms then spread proximally to affect both lower and upper extremities in a characteristic...
It was hypothesised that the administration of intravenous compared to 31% of the control group, had to stop chemotherapy. Only 4% of patients in the CaMg group, three different oxaliplatin-based protocols. Ninety-six patients with colorectal cancer were included who had been treated with 910 mg/m² in the CaMg group compared with 650 mg/m² in the remaining 65 patients served as a historic control group. The median cumulative administered oxaliplatin dose was 1 g and magnesium sulphate 1 g before and after oxaliplatin; the control group, showed signs of neurotoxicity of any grade. Similarly, grade 3 neurotoxicity was less frequently observed in the CaMg group (8% versus 20%, p = 0.003) and more patients with CaMg remained on chemotherapy after 9 months (15% versus 9%). The overall anti-tumour efficacy of treatment did not appear to be affected. In fact, patients were able to stay on therapy for a longer period of time, thus potentially enjoying prolonged benefit from oxaliplatin-based therapy.

Based on the above data, the North Central Cancer Treatment Group (NCCTG) developed a prospective randomised, placebo-controlled, double-blinded clinical trial (N04C7) to look at intravenous CaMg in patients receiving oxaliplatin-based adjuvant chemotherapy for colon cancer. This protocol was developed with plans for enrolling 300 patients.

While the NCCTG trial was accruing patients on the above noted trial, another trial was also addressing this issue. The CONCePT (Combined Oxaliplatin Neurotoxicity Prevention Trial) trial was developed using a 2 × 2 study design, to try to study potential means to reduce oxaliplatin-induced neurotoxicity by different chemotherapy scheduling options (intermittent oxaliplatin) and also by the use of CaMg. In mid-2007, an interim analysis of unadjudicated data presented to the independent data monitoring committee suggested that there was a significantly lower response rate in the group getting CaMg, versus the placebo group, which led to study closure and also concomitantly terminated the NCCTG trial N04C7. Subsequently, however, independent radiologic review of CT scans from the CONCePT trial delineated that the antitumour response rate was actually numerically higher in the group getting CaMg, than in the group receiving the placebo.

When the data from the double-blinded NCCTG CaMg trial (N04C7) were analysed, they revealed that there was less grade 2 or worse neurotoxicity in the patients receiving CaMg versus placebo (22% versus 41% by NCI Common Toxicity Criteria, p = 0.04, and 28% versus 51% by an oxaliplatin specific neuropathy scale, p = 0.02). In addition, data are also emerging from a French study, entitled ‘NEUROXA’, whereby 144 patients with colorectal cancer in the adjuvant and palliative setting were randomised, in a double-blind manner, to get CaMg versus a placebo. Early analyses of data from this trial have become available, revealing that objective response rates and survivals are equivalent in the two arms. This group also reported that there was substantially less neurotoxicity in one group versus the other (5% versus 24% of grade 3 NCI Common Toxicity Criteria, p < 0.001). The blind for this trial has not yet been broken.

Thus, there are data to support that CaMg is effective for preventing oxaliplatin-induced neurotoxicity and that this treatment does not interfere with oxaliplatin-based antitumour activity. More information should become available regarding this preventative treatment in the very near future.

### Table 1 – Chemotherapeutic agents causing peripheral neuropathy

<table>
<thead>
<tr>
<th>Platinum agents</th>
<th>Cisplatin</th>
<th>Carboplatin</th>
<th>Oxaliplatin</th>
<th>Vinca alkaloids</th>
<th>Vincristine</th>
<th>Vinblastine</th>
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<tr>
<td>Taxanes</td>
<td>Paclitaxel</td>
<td>Docetaxel</td>
<td>Epothilones</td>
<td>Ixabepalene</td>
<td>Newer agents</td>
<td>Bortezomib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thalidomide</td>
<td></td>
<td>Lenolidamide</td>
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</table>

‘glove and stocking’ distribution. CIPN has not been adequately characterised nor the pain quantified clinically and can occur at various points in the pathogenic process. Further details regarding how these different agents cause CIPN and the resultant symptoms have been discussed in recent review articles.

Compared to other neuropathies or neuropathic pain syndromes, there is a resemblance to diabetic neuropathy with similar glove and stocking distribution and other characteristics, such as pain, paraesthesias, and dysesthesias. However, treatments for diabetic neuropathies are not necessarily helpful for preventing or treating neuropathies associated with chemotherapy.

Given the prevalence of CIPN, and that it can be dose-limiting for several cytotoxic drugs, symptom control studies have been conducted looking at ways to prevent or alleviate established CIPN. Studies directed at both of these areas are reviewed below, with randomised trials being summarised in Tables 2 and 3.

### 2. Prevention of CIPN

#### 2.1. Calcium and magnesium infusions

It was hypothesised that the administration of intravenous calcium and magnesium (CaMg) might help prevent oxaliplatin-induced peripheral neuropathies, reasoning that increasing the concentration of extracellular calcium has been demonstrated to facilitate sodium channel closing and thus this would potentially decrease the observed oxaliplatin-induced hyperexcitability of peripheral neurons. In a retrospective, non-randomised study, 161 patients with advanced colorectal cancer were included who had been treated with three different oxaliplatin-based protocols. Ninety-six patients of this series received intravenous calcium gluconate 1 g and magnesium sulphate 1 g before and after oxaliplatin; the remaining 65 patients served as a historic control group. The median cumulative administered oxaliplatin dose was 910 mg/m² in the CaMg group compared with 650 mg/m² in the control group. Only 4% of patients in the CaMg group, compared to 31% of the control group, had to stop chemotherapy due to neurotoxicity (p = 0.000003). At the end of treatment, 27% of the CaMg group, versus 75% of the control group, showed signs of neurotoxicity of any grade. Laryngopharyngeal dysesthesias affected 9% of the control patients and were not reported in the patients receiving CaMg. Likewise, grade 3 neurotoxicity was less frequently observed in the CaMg group (8% versus 20%, p = 0.003) and more patients with CaMg remained on chemotherapy after 9 months (15% versus 9%). The overall anti-tumour efficacy of treatment did not appear to be affected. In fact, patients were able to stay on therapy for a longer period of time, thus potentially enjoying prolonged benefit from oxaliplatin-based therapy.

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Thus, there are data to support that CaMg is effective for preventing oxaliplatin-induced neurotoxicity and that this treatment does not interfere with oxaliplatin-based antitumour activity. More information should become available regarding this preventative treatment in the very near future.

#### 2.2. Vitamin E

There are data to suggest that vitamin E, a fat soluble vitamin classified as an antioxidant, may potentially decrease the
<table>
<thead>
<tr>
<th>Agent/Author</th>
<th>Number of patients</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pace 200312</td>
<td>47</td>
<td>CIPN in 31% patients with vitamin E versus 86% without ($p &lt; 0.01$)</td>
<td>Open label; cisplatin</td>
</tr>
<tr>
<td>Argyriou 200514</td>
<td>40</td>
<td>CIPN in 25% patients with vitamin E versus 73.3% without vitamin E ($p = 0.019$).</td>
<td>Open label; cisplatin, paclitaxel, or combination cisplatin/paclitaxel</td>
</tr>
<tr>
<td>Argyriou 200629</td>
<td>35</td>
<td>CIPN in 21% of patients with vitamin E group versus 66% without ($p = 0.026$).</td>
<td>Placebo-controlled; double-blinded cisplatin; results based on interim analysis of the first 50 patients, clinical trial ongoing</td>
</tr>
<tr>
<td>Pace 200713</td>
<td>81</td>
<td>Median CIPN score lower in the vitamin E group ($p &lt; 0.05$)</td>
<td></td>
</tr>
<tr>
<td>Calcium/Magnesium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nikcevich 200810</td>
<td>104</td>
<td>CIPN occurred in 22% versus 41% by NCI Common Toxicity Criteria ($p = 0.04$) and 28% versus 51% by an oxaliplatin specific neuropathy scale ($p = 0.02$)</td>
<td>Placebo-controlled; double-blinded oxaliplatin</td>
</tr>
<tr>
<td>Glutamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang 200723</td>
<td>86</td>
<td>Less grade 1–2 (17% versus 39%) and grade 3–4 CIPN after four cycles (5% versus 18%) and six cycles (12% versus 32%)</td>
<td>Open-label; oxaliplatin; no differences in chemotherapy response</td>
</tr>
<tr>
<td>Glutathione</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cascinu 200225</td>
<td>52</td>
<td>Significantly less peripheral neuropathy any grade cycles 4 and 8 ($p = 0.04$), as well as less grade 3–4 neuropathy at cycle 8 ($p = 0.01$)</td>
<td>Placebo-controlled; double-blinded; oxaliplatin; no differences in chemotherapy response</td>
</tr>
<tr>
<td>Smyth 199776</td>
<td>152</td>
<td>CIPN incidence significantly decreased in treatment arm (31%) versus control (75%) ($p=0.033$)</td>
<td>Placebo-controlled; double-blinded; cisplatin</td>
</tr>
<tr>
<td>Cassinu 199524</td>
<td>50</td>
<td>After 15 weeks, 4/24 treatment arm versus 16/18 placebo arm experienced neurotoxicity ($p = 0.0001$)</td>
<td>Placebo-controlled; double-blinded; cisplatin</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin 200677</td>
<td>14</td>
<td>5/7 patients in the control group and 0/7 in the treatment group experienced grade 2–4 neuropathy ($p &lt; 0.05$). The incidence of grade 2–4 neuropathy after 12 cycles of chemotherapy was significantly less in the treatment group ($p &lt; 0.05$).</td>
<td>Placebo-controlled; oxaliplatin</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argyriou 200629</td>
<td>40</td>
<td>Incidence of peripheral neuropathy was significantly decreased in treatment arm (31%) versus control arm (75%) ($p = 0.03$)</td>
<td>Open label; oxaliplatin</td>
</tr>
<tr>
<td>Xaliproden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cassidy 200650</td>
<td>649</td>
<td>17% of patients receiving xaliproden versus 11% of patients receiving placebo experienced grade 3 CIPN</td>
<td>Placebo-controlled; double-blinded oxaliplatin; no differences in chemotherapy response</td>
</tr>
<tr>
<td>Amifostine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leong 200334</td>
<td>66</td>
<td>Not effective</td>
<td>Placebo-controlled; double-blinded; paclitaxel and carboplatin</td>
</tr>
<tr>
<td>Hilpert 200571</td>
<td>72</td>
<td>Not effective</td>
<td>Placebo-controlled; double-blinded; paclitaxel and carboplatin</td>
</tr>
<tr>
<td>Nimodipine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cassidy 199836</td>
<td>51</td>
<td>Not effective</td>
<td>Placebo-controlled; double-blinded; neurotoxicity scores were significantly lower in placebo patients ($p = 0.002$)</td>
</tr>
<tr>
<td>Org 2766</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van der Hoop 199057</td>
<td>55</td>
<td>Vibration perception was maintained on both active arms compared to placebo</td>
<td>Placebo-controlled; double-blinded cisplatin</td>
</tr>
<tr>
<td>Roberts 199739</td>
<td>220</td>
<td>Not effective</td>
<td>Placebo-controlled; double-blinded; cisplatin; may increase the rate and degree of neuropathies ($p &gt; 0.05$)</td>
</tr>
<tr>
<td>Koeppen 200438</td>
<td>150</td>
<td>Not effective</td>
<td>Placebo-controlled; vincristine</td>
</tr>
<tr>
<td>rhuLIF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davis 200540</td>
<td>117</td>
<td>Not effective</td>
<td>Placebo-controlled; double-blinded; combination carboplatin/paclitaxel</td>
</tr>
</tbody>
</table>
incidence and/or severity of CIPN. A pilot study published by Pace et al.12 looked at the neuroprotective effect of Vitamin E for preventing CIPN in 47 patients receiving cisplatin chemotherapy who were randomised to receive either Vitamin E (alpha-tocopherol, 300 mg/d) with cisplatin treatment and for 3 months after therapy versus cisplatin treatment alone. In patients receiving vitamin E, they reported a significantly decreased incidence of peripheral neuropathy (31%, four of 13 patients) compared to those without vitamin E (86%, 12 of 14 patients).12 These investigators also presented an abstract at the ASCO 2007 meeting which consisted of randomised double-blind clinical trial data supporting that vitamin E decreased cisplatin-induced CIPN.13 This protocol studied patients receiving cisplatin chemotherapy who were randomised to vitamin E (alpha tocopherol 400 mg per day) versus placebo. The reported analysis was an interim one regarding the first 50 patients who had received cisplatin treatment in the short term (year 1), but not on longer term survival.17 Three of these studies that evaluated the effect of anti-oxidant supplementation with stage IIIb or IV non-small cell lung cancer without versus with stage IIIb or IV non-small cell lung cancer were examined.15,16 In one study,15 patients receiving supplementation with vitamin E (400 IU/d) and beta-carotene (30 mg/d) versus placebo during radiation therapy for head and neck cancer were examined. Because of ethical concerns regarding reports that beta-carotene supplementation may increase the risk of lung cancer, they stopped the use of beta-carotene early and continued with the use of vitamin E alone versus placebo. This study reported a higher local recurrence rate among the group supplemented with both beta-carotene and vitamin E, and a modestly increased rate of recurrence in the vitamin E alone arm.15 The other study16 looked at the use of vitamin E (400 mg) versus placebo as a mouth rinse for the prevention of radiation induced mucositis. There was a poorer overall and median survival rate in the vitamin E arm versus placebo arm (32% and 8.5 months versus 63% and 12.5 months, respectively). However, the authors acknowledge that one potential confounding factor in the differences in survival was the higher prevalence of stage III and IV patients in the vitamin E group.16

Nonetheless, data regarding the use of vitamin E with concurrent chemotherapy are more reassuring. A recent literature review conducted by Ladas et al.17 reported on six studies that evaluated the effect of anti-oxidant supplementation on survival and recurrence. Three of these studies found no effect on recurrence or survival, two reported a survival benefit, and one study reported an increase in survival in the short term (year 1), but not on longer term survival.17 Also reassuring, Leonetti et al.18 conducted a study evaluating the effects of vitamin E on anti-tumour therapy with cisplatin both in vitro and in vivo. They found no significant difference on cell survival between in vitro cells treated with cisplatin alone versus those with the addition of vitamin E. They also found that, in vivo, cisplatin alone reduced the tumour by 40% and the addition of vitamin E had no effect on tumour growth.18 Finally, a preclinical study by Pace et al.12 was reported regarding immunosuppressed nude mice implanted with a human-melanoma xenograft, who were treated with cisplatin alone versus cisplatin plus vitamin E. They found no differences in terms of tumour weight inhibition, tumour growth delay, or a difference in life span in the combination group compared to the cisplatin group alone.12

In addition, another randomised study19 reported the use of paclitaxel and carboplatin chemotherapy in 136 patients with stage IIIb or IV non-small cell lung cancer without versus with multiple high dose antioxidants (vitamin C, vitamin E, Table 3 – Randomised controlled trials for treatment of CIPN

<table>
<thead>
<tr>
<th>Agent/Author</th>
<th>Number of Patients</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriptyline Hambuck 200241</td>
<td>57</td>
<td>No CIPN benefit observed</td>
<td>Placebo-controlled; double-blinded; crossover; cisplatin</td>
</tr>
<tr>
<td>Amitriptyline Kautho 200842</td>
<td>44</td>
<td>No CIPN benefit observed</td>
<td>Placebo-controlled; double-blinded</td>
</tr>
<tr>
<td>Gabapentin Rao 200743</td>
<td>115</td>
<td>No CIPN benefit observed</td>
<td>Placebo-controlled; double-blinded; crossover</td>
</tr>
<tr>
<td>Lamotrigine Rao 200847</td>
<td>131</td>
<td>No CIPN benefit observed</td>
<td>Placebo-controlled; double-blinded</td>
</tr>
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</table>
and synthetic beta-carotene). They reported similar overall response rates (33% versus 37%), one year survivals (33% versus 39%), two year survivals (11% versus 16%), and median survivals (9 versus 11 months), respectively.19

To be more certain of the safety of using vitamin E with chemotherapy, it appears reasonable to conduct an additional trial to attempt to better clarify whether vitamin E will interfere with the anti-cancer activity of chemotherapy in a more homogenous group of patients receiving a uniform treatment programme. If the results of this trial are encouraging, then it may be reasonable to consider using vitamin E to prevent neurotoxic injury from neurotoxic chemotherapy agents.

2.3. Glutamine

The effectiveness of glutamine, known to up-regulate nerve growth factor mRNA in an animal model,20 as a neuroprotective agent was suggested in two pilot trials.21,22 Wang23 recently reported results of a small randomised, open label (with a no treatment control arm) study using glutamine for prevention of oxaliplatin-induced neuropathy. Eighty six patients were randomised to receive glutamine 15 mg twice daily for seven consecutive days every 2 weeks following oxaliplatin infusion (n = 42) or not to receive glutamine (n = 44). A significantly lower incidence of grade 3–4 neuropathy was noted in the glutamine group after four cycles (5% versus 18%; p = 0.05) and six cycles (12% versus 32%; p = 0.04). The need for oxaliplatin dose reduction was lower in the glutamine group and there were no significant between-group differences in response to chemotherapy or survival.24 While the results of this trial look promising, data are needed from a larger randomised placebo controlled trial, before it can be recommended for routine practice.

2.4. Glutathione and N-acetylcysteine

Glutathione has been shown to prevent the initial accumulation of platinum adducts in the dorsal root ganglia, which is the proposed mechanism for the development of neurotoxicity in patients receiving platinum agents. Two small randomised trials suggest that glutathione was beneficial for prevention of cisplatin24 and oxaliplatin-induced peripheral neuropathies,25 while another trial demonstrated that the addition of glutathione to cisplatin therapy reduced toxicity and allowed more cycles of treatment to be administered.26 N-acetylcysteine, an antioxidant drug which increases whole blood concentrations of glutathione, demonstrated a suggestion of benefit in preventing CIPN in patients receiving oxaliplatin in a small (14 patient) pilot study.27 Thus, the utility of glutathione and N-acetylcysteine looks promising but needs further validation.

2.5. Anti-epileptic agents

Carbamazepine, an antiepileptic agent that inhibits sodium channel activity, has been suggested to have a role in preventing oxaliplatin neuropathy based on its effect in reversing oxaliplatin-induced sodium channel dysfunction. Nonetheless, results of a pilot trial (n = 12) testing carbamazepine for this indication were not supportive of a benefit from this drug.28

Oxcarbazepine, a keto-analogue of carbamazepine which inhibits high-frequency firing of nerves without impairing normal impulse conduction and modulates both voltage-sensitive sodium channels and high voltage-activated N-type calcium channels, has also been identified as a candidate for preventing oxaliplatin-induced peripheral neuropathies. Results from a small randomised, open-label, controlled trial suggest that oxcarbazepine may protect against oxaliplatin-induced peripheral neuropathies.29 A larger placebo-controlled trial is needed to confirm these results.

2.6. Xaliproden

Results of a large randomised double blind placebo controlled phase III study (n = 649) assessed the efficacy of xaliproden, an orally administered non-peptide neurotrophic agent, for reducing oxaliplatin-induced CIPN. These results were reported at the ASCO 2006 meeting. An overall CIPN rate of 73–74% was reported in the two groups, with a lower incidence of grade 3 CIPN, 17% versus 11%, favouring the xaliproden. However, xaliproden did not reduce the overall incidence of neurotoxicity, but rather shifted 5% of patients from grade 3 to grade 2 neurotoxicity. The use of xaliproden in this trial was not associated with a higher cumulative oxaliplatin-dose or a longer time on therapy. In addition, no shorter time to recovery was noted with xaliproden, although it has to be noted that the drug was discontinued at the same time when the oxaliplatin-based therapy was stopped. Xaliproden did not appear to reduce cancer response rates.30 A phase III trial is ongoing to try and confirm these results and to investigate the benefit of continuing this agent after discontinuation of oxaliplatin.

2.7. Additional tested agents which do not appear to be effective for prevention of CIPN

Several small trials31–34 have addressed the potential efficacy of amifostine for protection against CIPN, with the end result being that recent American Society of Clinical Oncology (ASCO) clinical practice guidelines state that the available data do not support the use of amifostine for this indication.35 A small randomised placebo-controlled trial of nimodipine, a calcium channel antagonist, for prevention of cisplatin induced peripheral neuropathy was negative, with the suggestion that it may actually exacerbate neurotoxicity.36

Despite early preclinical data and clinical experience suggesting benefit from Org 276637 (an adrenocorticotropic hormone analogue) for prevention of cisplatin induced neuropathies, larger randomised placebo-controlled trials failed to demonstrate any reduction in peripheral neuropathy,38,39 with one trial actually suggesting that it may increase neuropathy.39

Lastly, Davis et al.40 reported data on 117 patients who were randomised to receive two doses of a recombinant human leukaemia inhibitory factor (rhuLIF) versus a placebo for prevention of carboplatin/paclitaxel-induced peripheral neuropathy, with negative results.40
3. Treatment of established CIPN

As opposed to trying to prevent CIPN, a number of randomised studies have been designed to find ways of treating established CIPN.

3.1. Tricyclic antidepressants

One of the first randomised, placebo-controlled, double-blinded clinical trials to look at the treatment of established CIPN was a relatively small one (n = 57) conducted by the NCCTG that studied the tricyclic antidepressant nortriptyline. The rationale for this trial was that tricyclic antidepressants had been shown in controlled trials to be effective in treating pain associated with diabetic neuropathy and other neuropathies. This trial, however, was unable to demonstrate any statistically significant improvement for nortriptyline, compared to a placebo, for chemotherapy-induced pain or paraesthesias. Another small randomised, double-blind, placebo-controlled study examined the efficacy of low-dose amitriptyline as treatment for CIPN, with patients receiving a maximum of 50 mg of oral amitriptyline (n = 22) versus placebo (n = 22) for 8 weeks, was also unable to demonstrate any benefit for this drug to improve neuropathic symptoms.

3.2. Gabapentin

A randomised, placebo-controlled, double-blinded NCCTG clinical trial studied the utility of gabapentin, an anticonvulsant structurally similar to the neurotransmitter gamma-aminobutyric acid (GABA). This drug had been shown to be effective in treating neuropathic pain from a variety of illnesses including diabetes, postherpetic neuralgia and post-amputation phantom pain syndromes. Gabapentin, and its newer analogue pregabalin, have been commonly used in clinical practice to treat symptoms of CIPN, in part due to anecdotal information suggesting potential utility. Nonetheless, this NCCTG randomised, double-blinded, placebo-controlled crossover trial (n = 115) illustrated that gabapentin was no better than placebo in ameliorating pain (p = 0.18) or symptoms of peripheral neuropathy (p = 0.38).

3.3. Lamotrigine

The NCCTG also evaluated another anticonvulsant, lamotrigine, based on reported data suggesting that this drug was effective for treating a number of neuropathic syndromes. This, again, was a randomised, double-blinded, placebo-controlled crossover trial (n = 131) which, likewise, was unable to show any CIPN improvement with lamotrigine over a placebo.

3.4. Topical baclofen, amitriptyline, and ketamine

Currently, the NCCTG is exploring another modality for treating established CIPN pain. This involves the use of a topical combination agent approach which potentially affords higher drug doses at sites of pain and thus, theoretically, has a greater chance of local effectiveness without undesirable systemic side effects. The treatment being studied is a combination product of baclofen, amitriptyline, and ketamine, representing three separate complementary mechanisms of action of pain control. This work is based on substantial preliminary data and positive clinical practice experience with this product. Results from this trial should be available by early 2009.

3.5. Acetyl-L-carnitine

Lastly, animal data suggest that acetyl-L-carnitine may be useful for prevention and/or reduction of paclitaxel-induced peripheral neuropathy. Bianchi et al. report positive pilot experience using this substance in 25 patients with grade 3 neuropathy receiving paclitaxel or cisplatin therapy. Further data are needed to validate these results.

4. The paclitaxel acute pain syndrome

This section will discuss a commonly appreciated paclitaxel toxicity which, to date, has not been well recognised as being a neurologic toxicity. This paclitaxel-induced toxicity is a bothersome syndrome of subacute aches and pains, that have been commonly referred to as arthralgias and myalgias; a symptom complex that has been described in up to 58% of patients receiving paclitaxel. These symptoms generally begin 1–3 days after drug administration and are usually self-limited, often resolving within 7 days. Symptoms have been described in large axial muscular and joint regions and generally are not accompanied by objective musculoskeletal or neurologic examination changes.

Recently, it was described that these pains occurring a few days after paclitaxel administration do not actually appear to be from injury to muscles or joints, but, rather, appear to be from neurologic injury. After learning that paclitaxel administered to animals causes nerve injury within 24 h of administration and subsequent questioning of patients about their symptom experience, this situation was recognised as likely being from a pathologic process affecting nerve tissue. This led to a small pilot project, whereby 18 Mayo Clinic patients, who noted the presence of subacute aches and pains following paclitaxel, were studied utilising structured interviews to characterise their symptoms. This work revealed that the pain symptoms typically began 1–2 days after the patients received paclitaxel and lasted for a median of 4–5 days. Pain was most commonly located in the back, hips, shoulders, thighs, legs and feet, with the most common descriptors used being ‘aching’ or ‘deep pain’. Commonly used adjectives to describe the pain were: radiating, shooting, aching, stabbing and pulsating. Some patients described increased pain with weight bearing, walking, or tactile contact. When directly asked whether the pains appeared to be specifically localised to either joints or muscles, 15 of 18 patients denied that this was the case.

Based on the nature and temporal occurrence of the paclitaxel acute pain syndrome symptoms, this manuscript hypothesised that the paclitaxel acute pain syndrome occurs as a result of sensitisation of nociceptors, their fibres or the spinothalamic system, as opposed to a musculoskeletal
injury. The symptom location, temporal relationship and self-limited nature of the syndrome make paclitaxel-induced acute pain syndrome distinct from the more chronic paclitaxel-associated peripheral neuropathy.59

The paclitaxel-induced acute pain syndrome following paclitaxel infusion has commonly been treated with non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and/or opioid pain medications. Few studies, mostly case series, have investigated the role of other medications in both prevention and treatment. Studies using Shakuyaku-Kanzo-To (a Japanese herb),62 antihistamines,63 corticosteroids,64 opioid analgesics65 and amifostine66 have not yielded enough evidence to establish a standard practice.

The only reported controlled, double-blinded prevention study evaluated glutamine, versus placebo, for the prevention of paclitaxel-induced acute pain.66 Glutamine was chosen as a study medication based on previous case reports that suggested that it was efficacious in this setting. This study involved patients who had received prior paclitaxel, who had reported troubles with sub-acute pain after this treatment, and who were still expected to receive at least two more cycles of the drug. Participants received 10 g of glutamine or a placebo three times per day for 5 days after their next dose of paclitaxel. Then, on their subsequent cycle of paclitaxel, they were crossed over to the opposite treatment. The primary endpoint was the change in severity or duration of the paclitaxel-induced acute pain. With a total of 46 patients accrued on this study, there were, unfortunately, no significant differences between the two groups for any of the pain ratings.66

Case series reports of two67 and ten68 patients have suggested that gabapentin can prevent the paclitaxel-induced acute pain syndrome. Despite the data noted above that demonstrate that gabapentin does not effectively alleviate the chronic CIPN associated with paclitaxel, the recent suggestion that paclitaxel-induced acute pain syndrome is, in fact, a process involving nociceptive fibres that, clinically, is distinct from paclitaxel-induced peripheral neuropathy, suggests a potential for the clinical utility of gabapentin in this situation. This supports the development of a randomised, placebo-controlled clinical trial to further investigate this potential.

5. Closing remarks

In closing, CIPN is a prominent clinical problem that is beginning to be investigated in some detail. It has recently become apparent that CaMg therapy can attenuate the development of oxaliplatin-caused CIPN. Whether this therapy will effectively attenuate CIPN from other cytotoxic agents is not known. Vitamin E may attenuate the development of CIPN, but more data regarding its efficacy and safety should be obtained prior to its general use in patients. Other drugs that look promising in preliminary studies, but need substantiation, include glutamine, glutathione, N-acetylcysteine, oxcarbazepine and xaliproden. An effective treatment of established CIPN, however, has yet to be found. Lastly, the paclitaxel acute pain syndrome appears to be caused by neurologic injury, as opposed to a pathologic process affecting muscles or joints. No drugs, to date, have been proven to prevent this toxicity.

Conflict of interest statement

None declared.

REFERENCES


