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Interventions for preventing neuropathy caused by cisplatin and related compounds

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Abstract

Background—Cisplatin and several related antineoplastic agents used to treat many types of solid tumors are neurotoxic, and most patients completing a full course of cisplatin chemotherapy develop a clinically detectable sensory neuropathy. Effective neuroprotective therapies have been sought.

Objectives—To examine the efficacy of purported chemoprotective agents to prevent or limit the neurotoxicity of cisplatin and related agents.

Search methods—We searched the Cochrane Neuromuscular Disease Group Specialized Register (25 August 2010), the Cochrane Central Register of Controlled Trials (Issue 3, 2010 in *The Cochrane Library*), MEDLINE (January 1966 to August 2010), EMBASE (January 1980 to August 2010), LILACS (January 1982 to August 2010), CINAHL (January 1982 to August 2010) for randomized trials designed to evaluate neuroprotective agents used to prevent or limit neurotoxicity of cisplatin and related agents among human patients.

Selection criteria—Quasi-randomized or randomized controlled trials whose participants received cisplatin (or related compounds) chemotherapy with or without a potential chemoprotectant (acetylcysteine, amifostine, ACTH, BNP7787, calcium and magnesium, diethyldithiocarbamate, glutathione, Org 2766, oxcarbazepine, or vitamin E) and were evaluated zero to six months after completing chemotherapy using quantitative sensory testing (primary) or other measures including nerve conduction studies or neurological impairment rating using validated scales (secondary).

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Contributions of Authors: All authors reviewed the selected literature. First drafts were prepared by Dr. Albers (amifostine), Dr. Cavaletti (Org 2766), and Drs. Chaudhry and Donehower (Glutathione, diethyldithiocarbamate, and vitamin E). Dr. Albers prepared the first draft of the report, which was reviewed, edited, revised, and approved by the other authors.

Declarations of Interest: Dr. Albers had research funding from Akzo Pharma Division, Organon, Inc. (1990-1993) as an investigator in a multicenter trial evaluating the efficacy of Org 2766 in the prevention or delay of cisplatin-induced neuropathy. Org 2766 is one of the interventions evaluated in this review. Dr. Cavaletti has acted as a paid consultant to Sigma-Tau IFR, Serono International SA, Rinat Neuroscience Co., Guilford Pharmaceuticals, and Eisai Pharmaceuticals, which manufacture different neuroprotective agents, and to Debiopharm SA which manufactures oxaliplatin. Drs. Chaudhry and Donehower had nothing to disclose.

Differences between Protocol and Review: In the most recent 2010 update we revised the risk of bias methodology according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

Data collection and analysis—We identified 16 randomized trials involving five possible chemoprotective agents in the initial 2006 review. Each study was reviewed by two authors who extracted the data and reached consensus. The 2010 update identified 11 additional randomized trials consisting of nine possible chemoprotective agents, including three treatments (acetylcysteine, calcium and magnesium, and oxcarbazepine) not among those described in the 2006 review. The included trials in the updated review involved eight unrelated treatments and included many disparate measures of neuropathy, resulting in insufficient data for any one measure to combine the results in most instances.

Main results—One of four eligible amifostine trials (541 total participants in all four trials) used quantitative sensory testing and demonstrated a favorable outcome in terms of amifostine neuroprotection, but the vibration perception threshold result was based on data from only 14 participants receiving amifostine who completed the post-treatment evaluation and should be regarded with caution. Of the six eligible glutathione trials (354 participants), one used quantitative sensory testing but reported only qualitative analyses. Four eligible Org 2766 trials (311 participants) employed quantitative sensory testing reported disparate results; meta-analyses of three trials using comparable measures showed no significant vibration perception threshold neuroprotection. The remaining trial reported only descriptive analyses. The single eligible trials involving acetylcysteine (14 participants), diethyldithiocarbamate (195 participants), calcium and magnesium (33 participants), and oxcarbazepine (32 participants) and the two eligible trials involving vitamin E (57 participants) did not perform quantitative sensory testing. In all, data from 1,537 participants were included.

Authors' conclusions—At present, the data are insufficient to conclude that any of the purported chemoprotective agents (acetylcysteine, amifostine, calcium and magnesium, diethyldithiocarbamate, glutathione, Org 2766, oxcarbazepine, or Vitamin E) prevent or limit the neurotoxicity of platin drugs among human patients.

Medical Subject Headings (MeSH)

Antineoplastic Agents [*adverse effects]; Cisplatin [*adverse effects analogs & derivatives]; Neuroprotective Agents [*therapeutic use]; Peptide Fragments [therapeutic use]; Peripheral Nervous System Diseases [chemically induced; *prevention & control]

MeSH check words

Humans

Background

Cisplatin (cis-diaminodichloroplatinum) was the first heavy metal used as an antineoplastic agent. It has been used since the early 1970s to treat several kinds of solid tumors, including lung, ovary, testis, bladder, head and neck, and endometrium (Mollman 1990; Prestayko 1979). Typical dosage regimes vary from 50 to 100 mg/m² given intravenously every three to four weeks, usually for about six cycles, based on clinical response and toxicity. Alternative schedules include 20 mg/m² daily for 5 days, or 20 mg/m² given weekly for about six weeks. Cisplatin is known to be toxic to the nervous system (Mollman 1990; van der-Hoop 1990; Von Hoff 1979; Cavaletti 2004) and exhibits preferential uptake in the dorsal root ganglia and produces a dose-related large fibre sensory neuropathy (neuronopathy). The sensory neuropathy most often becomes evident after a cumulative cisplatin dose of at least 300 mg/m², but occasional patients, especially those with risk factors, those with pre-existing neuropathy, and those with combination chemotherapy may develop symptoms after lower cumulative doses (Roelofs 1984; Windebank 1994). Most

patients completing a full course of cisplatin chemotherapy develop a symptomatic and clinically detectable sensory neuropathy. Symptoms, including unpleasant distal paresthesias (tingling in the extremities) and numbness, may appear as soon as one month after initiating treatment. Lhermitte's symptom (an electric shock-like sensation on bending the neck), likely caused by centripetal degeneration of posterior columns, has also been described. Associated signs include evidence of large fibre sensory loss (reduced vibration and joint position sensations) and diminished or absent muscle stretch reflexes (Roelofs 1984; Thompson 1984). Sensory ataxia (incoordination) may be disabling in those patients who have severe neuropathy. Small fibre sensation is spared or mildly diminished (decreased pin-pain sensation). Strength is generally normal. Symptoms and signs are symmetric and usually worse distally. Despite the high frequency of neuropathy among patients treated with cisplatin, relatively few patients develop functional impairment sufficient to interfere with activities of daily living. Nevertheless, neurotoxicity is a major reason that cisplatin is discontinued and the cumulative dosage limited, potentially reducing its chemotherapeutic efficacy. In an attempt to reduce the toxicity of platinum drugs, second and third generation tumor-inhibiting platinum compounds including carboplatin, oxaliplatin, nedaplatin, and lobaplatin have emerged. Carboplatin lacks the nephrotoxicity of cisplatin, and neurotoxicity also is thought to be considerably less than associated with cisplatin. Carboplatin is used to treat ovarian, small cell lung, and refractory testicular cancers. Oxaliplatin is now FDA and European Union approved for use in the treatment of metastatic colon cancer; neurotoxicity is the major dose-limiting adverse-event (Grothey 2003; Grothey 2004).

Quantitative measures of vibration perception threshold (VPT) and sensory nerve action potential (SNAP) amplitude are complementary means of evaluating large sensory fibres. Both measures have been used to document development and progression of cisplatin-induced neuropathy (Wald 1994). Sequential nerve conduction studies among patients receiving cisplatin chemotherapy demonstrate progressive reduction of SNAP amplitudes, with little or no change in motor nerve conduction studies and needle electromyography (EMG). Reduction of the SNAP amplitude is thought to be a relatively sensitive indication of early cisplatin-induced neurotoxicity. This objective change occurs early in the course of cisplatin neuropathy, often before development of symptoms or signs of sensory neuropathy. It is generally believed that most patients receiving cisplatin show a sequential decline in SNAP amplitude relative to baseline (Wald 1994; Wald 1995). A decline which exceeds 40 per cent from baseline is used by some as the physiological criterion for sensory neuropathy associated with chemotherapy toxicity (Molloy 2001). Sural nerve biopsy shows evidence of Wallerian-like axonal degeneration affecting the large myelinated fibres, with scant evidence of regeneration, consistent with damage at the level of the dorsal root ganglia. Unmyelinated fibres are spared (Krarup-Hansen 1993). Cisplatin-induced neuropathy stabilizes or improves after discontinuing cisplatin (Elderson 1989), but clinical and electrodiagnostic deterioration often progresses for a few weeks after completing cisplatin treatment (called 'coasting'). With higher cumulative dosages, however, residual nerve damage may persist for long periods of time.

Experimental models of cisplatin neurotoxicity confirm that the neuronal cell body within the dorsal root ganglion is the site of injury. Cultured rat embryo dorsal root ganglion models have been used to study the mechanisms of cisplatin neurotoxicity (Windebank 1994). Cisplatin reproducibly inhibits axonal growth in a dose-dependent manner that includes concentrations similar to those known to produce human toxicity. The mechanism of action is thought to be related to platinum binding to DNA and interfering with DNA synthesis. Cisplatin produced abnormalities in the nucleoli of spinal root ganglion cells of large and small neurons (Tomiwa 1986). The hypothesis that cisplatin-induced neuropathy may result from nuclear and nucleolar changes in the sensory ganglion cell body was confirmed in the rat (Cavaletti 1992). After chronic cisplatin administration, the spinal

ganglia and peripheral nerves showed severe damage of the spinal ganglia neurons with predominant involvement of the nucleus and nucleolus associated with a decrease in the cell size after chronic cisplatin administration. Changes also occurred in the sciatic and peroneal nerves with the features of axonopathy (Cavaletti 1992). These changes described in rats also have been confirmed in mice (Carozzi 2010 in press). In addition, Schmidt et al. (Schmidt 1995) showed in a mouse model that nerve growth factor (NGF) exerts a major effect on the metabolism of transmitters associated with nociception, pain and sensation in cervical dorsal root ganglia in various models of toxic neuropathy, including the neuropathy produced by cisplatin. Cisplatin specifically induced a significant decrease in the number of large- and medium-sized neurons in the dorsal root ganglia, indicating neuronal atrophy, a finding that correlated with a highly significant loss of neuropeptides in cervical dorsal root ganglia in mice (Schmidt 1995).

Prevention of cisplatin neurotoxicity

In most instances of cisplatin-induced neuropathy, the nerves only partially recover or do not recover at all. For this reason, effective neuroprotective therapies have been sought. As therapeutic strategies were developed to maximize cisplatin effectiveness, such as minimizing renal insufficiency, cumulative dose-related neuropathy emerged as a major dose-limiting toxicity (Gandara 1991). Attempts to modulate cisplatin dose schedules did not influence the intensity of the resultant neurotoxicity (Hilkens 1995). Additional means of optimizing the therapeutic index of cisplatin were sought, such as coadministration of chemoprotective or rescue therapies to reduce adverse side effects without reversing anti-tumor activity. An ACTH (4-9) analogue Org 2766, glutathione (GSH), amifostine, and various neurotrophic growth factors have all been tried in clinical and experimental models to prevent cisplatin-induced neurotoxicity, and reviews exist of the clinical pharmacology and therapeutic efficacy of several chemoprotectants (e.g. Links 1999). Acetyl-L-carnitine has recently been reported to have a neuroprotective effect in cisplatin and paclitaxel models (Pisano 2003). Both GSH and vitamin E have been tested in human trials with platinum drugs (Cascinu 1995; Cascinu 2002; Pace 2003; Smyth 1997). Although the precise mechanism of cisplatin-induced neurotoxicity is unknown, various agents have been proposed to protect the peripheral nervous system from such neurotoxicity. For example, amifostine, an organic thiophosphate that acts as a scavenger of oxygen free-radicals, shows selective protection of normal tissues (cytoprotective) against toxicities induced by radiation, alkylating agents, and platinum compounds without influencing the anti-tumor effects of these treatments (Planting 1999). Diethyldithiocarbamate (DDTC) is a chelating agent thought to bind and remove tissue-bound platinum without interfering with the anti-tumor activity of cisplatin (Gandara 1995). Glutathione (GSH) is a nucleophilic sulphur-containing tripeptide thiol thought to permit delivery of higher doses of cisplatin without producing the expected neurotoxicity, perhaps by preventing the initial accumulation of platinum adducts in the dorsal root ganglia (Cascinu 1995; Cascinu 2002). The neuropeptide Org 2766 is thought to potentially ameliorate cisplatin neuropathy by exerting trophic effects and enhancing endogenous nerve repair mechanisms (as opposed to directly protecting against cisplatin neurotoxicity) (van Gerven 1994). Vitamin E is an antioxidant thought to protect against cisplatin-induced oto- and nephrotoxicities and potentially to protect against neurotoxicity (Pace 2003). Acetylcysteine (*N*-acetylcysteine, NAC) is a nutritional supplement thought to increase whole blood concentrations of glutathione, a useful agent for preventing the initial accumulation of platinum adducts and clinical oxaliplatin-induced neurotoxicity (Lin 2006). BNP7787 (disodium 2, 2' dithio-bisethane sulfonate) was developed as a putative chemoprotective agent (Miller 2008). Calcium and magnesium infusions were proposed to act as chelators of oxalate, thereby reducing the effect of oxalate on voltage-gated sodium channels (Gamelin 2004). Oxcarbazepine resembles the antiepileptic drug carbamazepine and also blocks voltage-sensitive sodium

channels and certain calcium channels. Oxcarbazepine was developed as a neuroprotective agent against oxaliplatin-induced neuropathy, which is thought to reflect the alteration of voltage-gated sodium channels by oxalate, a metabolite of oxaliplatin (Argyriou 2006a).

Objectives

The objective is to systematically review the evidence from randomized controlled trials concerning the ability of chemoprotective agents to prevent or limit the neurotoxicity of cisplatin among human patients.

Methods

Criteria for considering studies for this review

Types of studies—We included all randomized or quasi-randomized controlled human trials in which the efficacy of any form of chemoprotective treatment used to prevent or limit the neurotoxicity of cisplatin (or related oncologic platinum compounds including oxaliplatin or carboplatin) was compared with placebo, no treatment, or other treatments.

Types of participants—Adult participants of either sex undergoing chemotherapy with cisplatin (or related oncologic platinum compounds including oxaliplatin or carboplatin) as an antineoplastic medication.

Types of interventions—We included in the review any form of chemoprotective treatment, such as acetyl-L-carnitine, acetylcysteine, ACTH, amifostine, BNP7787, calcium and magnesium, Org 2766, glutathione, oxcarbazepine, vitamin E, and growth factors, used to prevent or limit cisplatin-induced neurotoxicity.

Types of outcome measures

Primary outcomes: The primary outcome measure was the change in quantitative sensory testing (QST) results (e.g., vibration perception threshold (VPT). Measures of VPT have been used in several studies of cisplatin toxicity. Although VPT does not have the specificity of nerve conduction study results, the sensitivity of QST is likely similar to nerve conduction study results. Outcome was evaluated during an interval of zero to six months after completing or discontinuing chemotherapy. When more than one evaluation occurred during this interval, the one closest to three months after completing chemotherapy treatment was selected for the primary measure.

Secondary outcomes: Secondary outcome measures included nerve conduction study results (SNAP amplitude) and measures of neurological impairment. Any other available measure of impairment was considered, but priority was given to those clinical, functional, or electrodiagnostic measures that used a validated scale. Examples of secondary outcome measures included: (a) SNAP amplitude; (b) Clinical impairment measured by the neurological examination using a validated scale; (c) Functional measures of activities of daily living; (d) Information from toxicity rating scales, and serious adverse events of chemoprotective treatment, which were fatal, life threatening, or require prolonged hospital admission. Secondary outcomes also were evaluated in terms of each of the zero to six month period after completing or discontinuing chemotherapy.

Search methods for identification of studies

Electronic searches—We searched the Cochrane Neuromuscular Disease Group Specialized Register (25 August 2010), the Cochrane Central Register of Controlled Trials (Issue 3, 2010 in *The Cochrane Library*), MEDLINE (January 1966 to August 2010),

EMBASE (January 1980 to August 2010), LILACS (January 1982 to August 2010) and CINAHL (January 1982 to 25 August 2010). The 2010 update followed the same strategy.

The searches were based on the following search strategy: (1) Cisplatin (adverse effects, toxicity, or therapeutic use) or cis-diamminedichloroplatinum, or platinum compounds or organoplatinum compounds or oxaliplatin or carboplatin AND (2) Neuroprotective agents or chemoprotectant or protective agents or Org 2766 or corticotropin (analogs & derivatives) or glutathione or amifostine or growth factors or nerve growth factor or neurotrophin or antidotes or vitamin E or acetyl-L-carnitine. Our search strategy was not restricted by language. In the initial and updated review, we did not approach pharmaceutical companies, but, in a few instances, we did contact the authors of the trials for additional information. We did not formally screen the references of the selected papers.

For electronic search strategies, see Appendix 1; Appendix 2; Appendix 3; Appendix 4; and Appendix 5.

Data collection and analysis

Selection of studies—The titles and abstracts identified from the register in the initial review were independently checked by two authors (JA and VC) to select potential articles for inclusion; agreement by both authors was achieved that resulted in 39 articles for inclusion. The full text of all potentially relevant studies was obtained for independent assessment by two authors for each article (among JA, GC, VC, and RD). The authors decided which studies fitted the inclusion criteria and graded their methodological quality. Disagreements about inclusion (three studies) were resolved by communication between the two authors, resulting in consensus. In the 2010 update, the titles and abstracts identified from the register in the initial review were independently checked by two authors (JA and GC) to identify potential articles for review; agreement by both authors was achieved. All authors reviewed the resulting list of articles recommending for full review or exclusion, resulting in selection of eleven articles for full review.

Data extraction and management—Data extraction was performed by two authors for each article and checked by a third author (JA) to identify differences of opinion. We began by separating the studies into treatment categories: amifostine, glutathione, DDTC (diethyldithiocarbamate), Org 2766, and vitamin E. The last two categories included only one article each. We assigned two authors to each of the categories (combining DDTC and vitamin E). We next tabulated whether or not individual studies showed dose-response efficacy (if more than one dose was studied). We summarized the types of outcomes reported (QST, nerve conduction studies, clinical, functional measure).

Assessment of risk of bias in included studies—We assessed risk of bias using the Cochrane Collaboration risk of bias tool, described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). We considered the adequacy of studies in the following domains: sequence generation, allocation concealment, blinding (subject, observer and assessor), incomplete outcome data addressed, selective reporting and other sources of bias. We used the assessments 'Yes' to indicate a low risk of bias, 'No' a high risk of bias and 'Unclear' where there was insufficient information to make a judgment (or when the criterion did not apply to the study). At least two authors evaluated each study and consensus agreement was reached. We included consideration of serious adverse events and determined if information on cost benefits was available.

Data synthesis—Few of the studies used a common outcome measure, and it was not possible to calculate a weighted treatment effect across trials, or to express all of the results as relative risks.

Results

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

The initial search identified 135 articles. From these, we selected 39 articles for complete review. The review identified 16 articles fulfilling inclusion criteria. The 2010 search identified 275 articles (including many duplications and previously identified), from which we selected 11 new studies for complete review. The combined articles involved the following potential chemoprotectant treatments:

- Acetylcysteine (one study). Acetylcysteine is a nutritional supplement thought to increase whole blood concentrations of glutathione, a useful agent for preventing the initial accumulation of platinum adducts and clinical oxaliplatin-induced neurotoxicity (Lin 2006).
- Amifostine (five studies). Amifostine is an organic thiophosphate described as a broad-spectrum cytoprotective agent potentially able to protect normal tissues from cytotoxic effects of chemotherapeutic agents (Kanat 2003).
- Calcium and magnesium (one study). Calcium and magnesium infusions may chelate oxalate (a metabolite of oxaliplatin), thereby reducing the effect of oxalate on voltage-gated sodium channels (Ishibashi 2010).
- Diethyldithiocarbamate (DDTC) (one study). DDTC is a heavy metal chelating agent and has been reported to reduce the incidence and severity of cisplatin-induced neuropathy (Gandara 1995).
- Glutathione (GSH) (six studies). The mechanism of neurotoxicity from platinum drugs is thought to be the accumulation of platinum within the dorsal root ganglia. The thio nucleophilic region of reduced GSH has high affinity for heavy metals and may be able to prevent the accumulation of platinum in the dorsal root ganglia.
- Org 2766 (four studies). Org 2766 is an ACTH (4-9) analogue which has been reported to reduce the incidence and severity of cisplatin-induced polyneuropathy (van-der-Hoop 1990).
- Oxycarbazepine (one study). Oxycarbazepine resembles the antiepileptic drug carbamazepine and also blocks voltage-sensitive sodium channels and certain calcium channels. It was developed as a neuroprotective against oxaliplatin-induced neuropathy, which is thought to reflect the alteration of voltage-gated sodium channels by oxalate, a metabolite of oxaliplatin (Argyriou 2006).
- Vitamin E (two studies). Vitamin E, an antioxidant protecting against free-radical injury, may be protective against cisplatin-induced polyneuropathy. Based on the observation that deficiency of vitamin E produces a pattern of peripheral neuropathy similar to cisplatin induced toxic neuropathy and the fact that decreased plasma vitamin E levels are observed in patients with cisplatin neuropathy, trials of vitamin E for prevention of toxic neuropathy have been done (Pace 2003).

The characteristics of the individual studies, including the quality attributes, are summarized in the table Characteristics of included studies.

Acetylcysteine (N-acetylcysteine, NAC)—Our 2010 update identified one article fulfilling the selection criteria and reporting the results of a randomized controlled trial designed to evaluate the protective effects of NAC against oxaliplatin-induced neurotoxicity (Lin 2006). This study, described as a “pilot study,” involved only a small number of participants. Oxaliplatin dose was discontinued or dose reduced to 75% of previous dose if the patients developed NCI grade 3 or 4 neuropathy or hand NCI grade 1 neuropathy respectively. Additionally, calculation of the score was arbitrarily modified (sum of worst neurological toxicity divided by number of assessable patients at each dose level).

- oxaliplatin for colorectal cancer (5 NAC treated and 9 placebo control participants) (Lin 2006)

Oral NAC (1,200 mg) was given one and one-half hours before each oxaliplatin administration, occurring every two weeks for up to 12 treatment cycles.

Amifostine—Our search identified five articles describing a total of four studies fulfilling the selection criteria and reporting the results of randomized controlled trials designed to evaluate the protective effects of amifostine against chemotherapy neurotoxicity. Two articles with different first authors (Kemp 1996; Rose 1996) described the same trial and were considered together for this review. The remaining four eligible trials included 271 amifostine treated participants and 270 control participants. These trials included participants being treated with;

- cisplatin for advanced head and neck cancer (37 amifostine treated participants and 37 control participants) (Planting 1999);
- paclitaxel and carboplatin for non-small cell lung cancer (19 amifostine treated and 19 control participants) (Kanat 2003);
- paclitaxel and carboplatin for ovarian cancer (93 amifostine treated and 94 control participants) (Lorusso 2003); and
- cisplatin and cyclophosphamide for advanced ovarian cancer (122 amifostine treated and 120 control participants) (Kemp 1996).

The amifostine regimens varied only slightly among trials, and all participants randomised to the amifostine groups received intravenous amifostine immediately before chemotherapy at doses of 740 mg/m² (Planting 1999) or 910 mg/m² (Kanat 2003; Kemp 1996; Lorusso 2003). All trials involved scheduled treatments of up to six cycles of chemotherapy, either weekly (Planting 1999) or at three week intervals (Kanat 2003; Kemp 1996).

Calcium and magnesium (Ca/Mg)—The 2010 update identified one article fulfilling the selection criteria and reporting the results of a randomised controlled trial to evaluate the protective effects of calcium and magnesium infusions against oxaliplatin neurotoxicity (Ishibashi 2010). The trial included participants being treated with 6 cycles of FOLFOX, which includes oxaliplatin (85 mg/m²) every two weeks.

- oxaliplatin for metastatic colorectal cancer (17 Ca/Mg treated and 16 control participants) (Ishibashi 2010).

Ca/Mg (850 mg/720 mg, respectively) was administered before and after infusion of oxaliplatin or placebo. In addition to oxaliplatin, FOLFOX chemotherapy includes administration of 5- fluorouracil and l-leucovorin with each of six, two week treatment cycles.

Diethyldithiocarbamate (DDTC)—Our search identified only one article fulfilling the selection criteria and reporting the results of a randomised controlled trial designed to

evaluate the protective effects of DDTC against cisplatin neurotoxicity (Gandara 1995). The trial included participants being treated with six courses of 100 mg/m² cisplatin every four weeks at 1.6 G/m².

- Cisplatin for ovarian, small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC) (data available for 96 DDTC treated participants and 99 control (placebo treated) participants (Gandara 1995).

DDTC, at 1.6 G/m², was administered 15 minutes before the start of cisplatin. In addition to cisplatin, other chemotherapies used were etoposide 100 mg/m² days 1, 2, 3 for SCLC and NSCLC and cyclophosphamide 750 mg/m² for ovarian carcinoma as six courses every four weeks.

Glutathione (GSH)—Our search identified six articles fulfilling the selection criteria and reporting the results of randomised controlled trials designed to evaluate the protective effects of GSH against platinum drugs (cisplatin and oxaliplatin) neurotoxicity. The six trials included prospective, randomised, and placebo controlled studies of a total of 354 participants (177 in intervention group and 177 in the control group). The two platinum drugs used were cisplatin (137 and 138 respectively in each group and oxaliplatin (40 in the intervention group and 39 in the control group). The dose of cisplatin was variable (from 40 to 100 mg/m²) and oxaliplatin 100 mg/m² for every 1 to 2 weeks for 3 to 9 weeks.

These trials included participants being treated with;

- cisplatin for ovarian cancer (27 GSH treated participants and 27 control participants) (Bogliun 1996);
- cisplatin for ovarian cancer (25 GSH treated participants and 25 control participants) (Cascinu 1995);
- oxaliplatin for colorectal cancer (26 GSH treated participants and 26 control participants) (Cascinu 2002);
- oxaliplatin for colorectal cancer (14 GSH treated participants and 13 control participants) (Milla 2009)
- cisplatin for non-small cell lung cancer (NSCLC) and head and neck cancer (11 GSH treated participants and 9 control participants) (Schmidinger 2000); and
- Cisplatin for ovarian cancer (74 GSH treated participants and 77 control participants) (Smyth 1997).

The GSH dose was variable from 1.5 G/m² to 5 G before chemotherapy. The end points used were a toxicity score (National Cancer Institute (NCI)/World Health Organization (WHO)) in all participants; functional scales (Hospital Anxiety and Depression (HAD) and Rotterdam scales) in 151 participants; Neuropathy Impairment Scale/Neuropathy Symptom Scale (NIS/NSS) in 54 participants; sensory nerve conduction studies (sural, median, or ulnar) in 156 participants; motor nerve conduction studies in 20 participants; and VBT testing in 54 participants.

Org 2766—Our search identified four articles fulfilling the selection criteria and reporting the results of randomized controlled trials designed to evaluate the protective effects of Org 2766 against cisplatin neurotoxicity. The four trials included 188 Org 2766 treated participants and 123 control participants. These trials included participants being treated with;

- cisplatin and cyclophosphamide for epithelial ovarian cancer (33 Org 2766 treated participants and 22 control participants) (van-der-Hoop 1990);

- cisplatin and cyclophosphamide for epithelial ovarian cancer (7 Org 2766 treated and 11 control participants) (Hovestadt 1992);
- cisplatin and different combinations of etoposide, bleomycin and ifosfamide for testicular and adenocarcinoma of unknown primary (19 Org 2766 treated and 23 control participants) (van Gerven 1994); and
- Cisplatin and cyclophosphamide for epithelial ovarian cancer (129 Org 2766 treated and 67 control patients) (Roberts 1997).

The Org 2766 regimens largely varied among trials in the range 0.25 to 4.0 mg/kg. All participants randomized to the Org 2766 groups received subcutaneous Org 2766 before and one hour after cisplatin in one trial (Roberts 1997), before and 24 hours after cisplatin in two trials (Hovestadt 1992; van-der-Hoop 1990) and during the daily course of cisplatin administration in one trial (van Gerven 1994). All trials involved scheduled treatments of up to nine cycles of chemotherapy, at three (Hovestadt 1992; van-der-Hoop 1990; van Gerven 1994) or three-to-four week intervals (Roberts 1997). Cisplatin was administered at different doses/cycle: 75 mg/m² (Hovestadt 1992; van-der-Hoop 1990), 75 to 100 mg/m² (Roberts 1997) or 100 mg/m² (van Gerven 1994).

Oxycarbazepine (OXC)—Our search identified one article fulfilling the selection criteria and designed to evaluate the protective effects of OXC against cisplatin neurotoxicity (Argyriou 2006a). The trial was prospective and randomized but without a placebo control arm (control patients were untreated). This trial included 40 participants being treated with cisplatin for colon cancer of which 20 were randomized to receive OXC, 600 mg twice a day and 20 were randomized to receive no treatment. The cumulative oxaliplatin dose after 12 courses was similar in both groups (1,782 OXC versus 1,750 control). Ultimately, 16 participants in each group completed the trial, and data from the 32 participants were available for analysis. Neurological symptoms and neurophysiological testing (sural, superficial peroneal, and ulnar SNAP and peroneal motor responses) were recorded at baseline and after 4, 8, and 12 courses of chemotherapy (e.g., the last studies performed at completion of 24 weeks of treatment).

Vitamin E—Our original search identified only one article fulfilling the selection criteria of randomized controlled trial to assess the protective effect of Vitamin E against cisplatin neurotoxicity. The 2010 update identified a second trial of similar design. Both trials were prospective and randomized studies without a placebo control arm (control patients were untreated). Both studies included participants being treated with cisplatin for various solid tumors (lung, ovarian, rhinopharynx, gastric, testicular, esophagus, ethmoid, and tongue cancer). The 2010 update identified a third randomized controlled trial involving the use of Vitamin E (Pace 2010), but the substantial participant dropout rate excluded the intention-to-treat analyses.

- Cumulative cisplatin dose was > 300 mg/m²; 13 vitamin E treated participants and 14 control participants) (Pace 2003). Alpha tocopherol (vitamin E) was used at dose of 300 mg/day starting before cisplatin and continuing up to three months after cisplatin treatment. Neurological symptoms and signs (by unmasked neurologists) were recorded and neurophysiological testing (sural and median sensory nerves) were done at baseline, after three cycles, and after completion of chemotherapy. A cumulative toxicity score was assigned.
- Six courses of cisplatin chemotherapy in various doses (Argyriou 2006). The treatment protocols were specific for the individual cancers, and all included chemotherapy agents in addition to cisplatin. Of note, five participants with gastric cancer also received docetaxel, another potential neurotoxicant (2 vitamin E group

and 3 controls). Thirty-five participants were enrolled; of which 30 completed the trial, of which 14 participants received vitamin E (600 mg/day) starting before cisplatin and continuing up to three months after cisplatin treatment. Neurological symptoms and signs (by unmasked neurologists) were recorded and neurophysiological testing (sural and median sensory nerves) were done at baseline, after three cycles, and after completion of chemotherapy.

Risk of bias in included studies

The risk of bias information for each study is summarized in Figure 1.

Acetylcysteine (N-acetylcysteine, NAC)—The single trial had adequate baseline and follow-up NCI neurotoxicity assessment; although electrophysiologic assessment, the nerve conduction study data was only described qualitatively (Lin 2006), indicating no electrophysiological change in acetylcysteine group without available data for the control group. The method of randomization and of allocation concealment was unclear. It also was unclear whether the study was blinded to participants, investigators, or outcome assessors.

Amifostine—All four trials had adequate baseline and follow-up assessments that occurred after completing chemotherapy within the intended zero to six month window. All four trials also included assessment following the last treatment cycle, with adequate follow-up to that point. Two trials (Kemp 1996; Planting 1999) included additional assessments up to three months after the last treatment cycle. The method of randomization was deemed secure and allocation concealment adequate for one trial (Lorusso 2003) but unclear for the remaining three trials. None of the four trials clearly masked the participant or the observer, and only one study (Kemp 1996) stated that the outcome assessor was blinded to the treatment group or to adverse events reported by the participant. The adequacy of analyses was deemed adequate for three studies but unclear for one (Planting 1999).

Calcium and magnesium (Ca/Mg)—The single trial had adequate baseline and follow-up assessments that occurred after completing chemotherapy within the intended zero to six month window, with assessment occurring immediately after the sixth treatment cycle (10 weeks). The method of randomization was deemed secure, and allocation of concealment and subject, observer, and outcome assessor blinding appeared adequate. An unavoidable limitation of the study was that enrolment was discontinued after 33 participants were entered into the study because the interim analyses showed poorer results in the Ca/Mg group (early termination of enrolment).

Diethyldithiocarbamate (DDTC)—In the single DDTC study (Gandara 1995), the methods of randomization and allocation concealment methods were unclear, although the subject blinding was adequate. Observer and outcome assessor blinding were considered inadequate. A large number of withdrawals (40 in the intervention arm and 71 in the control arm) were noted for progressive disease or toxicity.

Glutathione—All six trials had adequate baseline and follow-up assessments that occurred after completing chemotherapy within the intended zero to six month window. The method of randomization was deemed secure, allocation concealment was adequate, and blinding was done for subjects and observers in three trials (Cascinu 1995; Cascinu 2002; Smyth 1997) but not for the remaining three trials (Bogliun 1996; Milla 2009; Schmidinger 2000). Outcome blinding was adequate for four trials (Bogliun 1996; Cascinu 1995; Cascinu 2002; Smyth 1997) and unclear in the other two (Milla 2009; Schmidinger 2000). The adequacy of analyses was deemed adequate for five studies (Bogliun 1996; Cascinu 1995; Cascinu 2002; Milla 2009; Smyth 1997) and inadequate for one (Schmidinger 2000).

Org 2766—All four trials had adequate baseline and follow-up assessments that occurred after completing chemotherapy within the intended zero to six month window. One trial (Hovestadt 1992) included additional assessments up to 24 months after the last treatment cycle. The method of randomization was deemed secure and allocation concealment adequate for one trial (van-der-Hoop 1990) but unclear for the remaining three trials. Subject and outcome assessor blinding was adequate in three trials (Hovestadt 1992; Roberts 1997; van-der-Hoop 1990) and unclear in one (van Gerven 1994), while observer blinding was adequate in two trials (Roberts 1997; van-der-Hoop 1990) and unclear in two (Hovestadt 1992; van Gerven 1994). The adequacy of analyses was deemed adequate for one study (Roberts 1997) but unclear for two trials (Hovestadt 1992; van Gerven 1994) and inadequate for one (van-der-Hoop 1990).

Oxycarbazine (OXC)—Out of 40 participants enrolled in the single OXC study (Argyriou 2006a), eight dropped out (4 in each arm), mainly for disease progression plus two for adverse symptoms related to OXC treatment. The specific method of randomization was unclear, but the details were known only to the randomizations coordinator and concealed from the data analysts. Participants were not blinded, as this was an open label study. The dropout rate was not considered excessive, and the analyses were performed both on an intention-to-treat and completion-of-trial basis.

Vitamin E—Out of 47 participants enrolled in the initial vitamin E study (Pace 2003), 20 participants dropped out, mainly for disease progression. Twenty-seven participants, all of whom completed six cycles of cisplatin chemotherapy and received a cumulative dose of cisplatin $> 300 \text{ mg/m}^2$, were available for analysis. Individual doses and combinations of chemotherapy varied. Method of randomization, allocation concealment, and blinding were unclear. Insufficient details were provided on withdrawals, dropouts, losses to follow-up and the analysis was thought to be unclear in this respect. A modified total neuropathy scale was used, but this modified version is not a validated measure. In the second study (Argyriou 2006), 5 of the 37 enrolled participants dropped out because of death or disease progression. Thirty participants completed the chemotherapy protocol; the mean total cisplatin dose was comparable in the vitamin E and control groups ($120.6 \pm 5.2 \text{ mg}$ and $121.9 \pm 3.4 \text{ mg}$, respectively). The precise randomization method was not described but the allocation concealment appeared adequate, with the details of the randomization known only to the randomization coordinator. In this open label study, the subjects were not blinded but those performing the evaluations were blinded, as were the outcome assessors.

Effects of interventions

The results of the review for each potential chemoprotective agent follow.

Acetylcysteine (N-acetylcysteine, NAC)

Primary outcome measure: No primary outcome measure was available in the single NAC study (Lin 2006).

Secondary outcome measures

(1) Nerve conduction measures of sensory response amplitudes: Sensory (sural SNAP) amplitude, distal latency, and conduction velocity, and motor (median CMAP) amplitude, distal latency, conduction velocity, and F wave latency were measured at baseline and after 4, 8, and 12 cycles of chemotherapy. However, the data were only reported for the NAC group, indicating no significant deterioration over the full trial (something they attributed to NAC), without reporting similar data for the control group.

(2) Clinical impairment on neurological examination using a validated scale: A complete neurological examination was performed by a neurologist but data were not reported, aside from noting (in the Discussion) that oxaliplatin-induced neurotoxicity is characterized by a rapid-onset acute sensory neuropathy.

(3) Functional activities of daily living: None was included.

(4) Information from toxicity rating scales: Toxicity due to possible sensory neuropathy was assessed every two weeks using the common toxicity criteria (CTC) of the NCI toxicity rating scale. After 12 cycles of treatment, the incidence of Grade 1, 2, and 3 neurotoxicity was 80, 20, and 0% among the 5 participants in the NAC group, respectively, and 100, 89, and 33% in the control group ($P = 0.01$).

Adverse effects attributed to the study intervention: Adverse effects were reported in all study participants with severe adverse events in 27 control group and 30 of DDTC arm. Twenty-two in the DDTC and nine in control group withdrew because of toxicity.

Details of other outcomes not specified in the protocol: None described.

Amifostine

Primary outcome measure: QST was used as an outcome measure in a single amifostine trial (Planting 1999), although only mean baseline and post-treatment values and non-parametric analyses were reported. This trial involved 74 participants with advanced neck cancer who were treated with six cycles of weekly cisplatin (70 mg/m^2). Cisplatin neurotoxicity was measured by VPT recordings made from the second metatarsal bone of each hand (test of large sensory axons and receptors). An increased threshold indicates worsening sensory performance. Three measurements of the VPT (in micrometers of skin displacement) were recorded for each hand and the mean taken as the VPT for each side. Participants receiving pre-treatment with amifostine (740 mg/m^2) prior to cisplatin administration (37 participants) showed significantly less subclinical neurotoxicity as measured by the VPT relative to control participants receiving cisplatin only (37 participants). Although the groups were similar in terms of most measures, a slightly smaller number of participants (borderline significant) in the amifostine group relative to the control group completed six cycles of cisplatin (20 versus 28; P value = 0.07). The VPT analyses, which were based on participants in whom a three-month post-treatment VPT value was available, included 14 participants in the amifostine group and 20 participants in the control group. The mean VPT increased at three months compared to baseline values for both groups, but the increase was smaller for the amifostine group compared to the control group (left hand, 0.15 versus 0.48, mean difference 0.33 (95% CI -0.01 to 0.67); right hand 0.18 versus 0.40, mean difference 0.12 (95% CI -0.03 to 0.27). The authors explained that the borderline significant group difference for the right hand VPT reflected an imbalance at baseline for the groups and limited data.

Secondary outcome measures

(1) Nerve conduction measures of sensory response amplitudes: This secondary outcome measure was used in a single trial evaluating the protective effect of amifostine against neurotoxicity of carboplatin (area under the curve according to the Calvert formula) and paclitaxel (175 mg/m^2) among participants with non-small cell lung cancer (Kanat 2003). Chemotherapy-induced neurotoxicity was assessed by serial SNAPs recorded from the right sural, left ulnar, and right median sensory nerves. Evaluations were performed at baseline and immediately after the sixth cycle of treatment. Participants who received pre-treatment with amifostine (910 mg/m^2) prior to chemotherapy (19 participants) were compared to

control participants who received chemotherapy only (19 participants). The mean SNAP amplitudes for both groups were comparable at baseline and also after six cycles of chemotherapy. There was no significant decline in the mean amplitudes for either group after treatment.

(2) Clinical impairment on neurological examination using a validated scale: There was no use of a uniform or standardized neurological examination scale among the studies, but several clinical scales were used that were based on descriptions of conventional neurological symptoms or signs. For example, clinical neurotoxicity “grade 1” developed in 4 of 37 participants in the cisplatin plus amifostine group and 5 of 37 participants in the cisplatin only group (risk ratio 0.80, 95% CI 0.23 to 2.75) (see Analysis 1.1) (Planting 1999). Conversely, paresthesias “grade 2” (reflecting an adverse sensory symptom outcome) developed in 8 of 19 participants in the carboplatin and paclitaxel plus amifostine group compared to 18 of 19 in the carboplatin and paclitaxel only group (risk ratio 0.59, 95% CI 0.36 to 0.98) (Kanat 2003). Neurotoxicity as evaluated by a clinical examination and scored as “grade 3-4” (not further described) was reported among 93 participants receiving carboplatin and paclitaxel plus amifostine at any of the scheduled evaluations in 19 of 508 evaluations (3.7%) versus in 37 of 514 evaluations (7.2%) among participants receiving carboplatin and paclitaxel only (Lorusso 2003). Our review protocol was interested in results after treatment was completed. Data recorded after the last treatment cycle are not available in the Lorusso et al. article (Lorusso 2003), but, despite a similar proportion of subjects in each group who continued to show an adverse effect, the neurotoxicity comparisons for the last three cycles of chemotherapy no longer showed a substantial group difference (10 of 244 evaluations (4%) in the amifostine group and 23 of 245 evaluations (9%) in the control group). Furthermore, the data were reported as adverse neurotoxicity occurring during any of the treatment cycles, and therefore include multiple observations from individual patients, not independent observations, precluding further evaluation.

(3) Functional activities of daily living: Based on a sensorimotor neurotoxicity score, Kanat et al. (Kanat 2003) reported a minor (“grade 2”) decrease in the activities of daily living score in 2 of 19 participants in the carboplatin and paclitaxel plus amifostine group compared to 9 of 19 participants in the carboplatin and paclitaxel only group (risk ratio of 0.22, 95% CI 0.06 to 0.90) (see Analysis 2.1).

(4) Information from toxicity rating scales: Kemp et al. reported that the incidence of neurotoxicity, defined as symptoms of peripheral neuropathy or as a decrease in the neurological function daily activity score, was related to the cumulative dose of cisplatin among participants with ovarian cancer who were treated with cisplatin and cyclophosphamide (Kemp 1996). By treatment cycle 5, there was a significant difference ($P = 0.015$) between the groups, favoring the amifostine group. Following the last treatment cycle, the NCI neurologic toxicity rating (grades 0, 1, 2, or 3) was significantly reduced ($P = 0.029$) by pre-treatment with amifostine (122 participants pretreated with amifostine, 120 control participants). Although the risk of developing any level of neurotoxicity (grade 1, 2, or 3) was almost significantly reduced by pre-treatment with amifostine relative to no treatment (risk ratio of 0.81, 95% CI 0.66 to 1.00) (see Analysis 14.1), the risk of developing severe (grade 3) neurotoxicity was not significantly reduced by pre-treatment with amifostine (risk ratio of 0.59, 90% CI 0.27 to 1.30) (see Analysis 14.2). None of the participants in the amifostine group but two of the participants in the control group discontinued cisplatin because of neurotoxicity.

Adverse effects attributed to the study intervention: Hypotension occurred during 133 of 508 amifostine infusions (26%; 95% CI 23.5 to 23.8%) in the trial reported by Lorusso, et

al. (Lorusso 2003). However, the degree of hypotension was generally mild and well tolerated and led to a reduction of the amifostine dose from 910 mg/m² to 740 mg/m² in subsequent cycles after only 18 of the 133 occurrences (14%). Similarly, the study reported by Kanat et al. (Kanat 2003) reported that hypotension occurred in 5 of 19 participants (26%) during the first or second administration of amifostine; lowering the subsequent dose from 910 mg/m² to 740 mg/m² for these participants again eliminated the problem. In the study reported by Planting et al. (Planting 1999), hypotension was observed during amifostine infusion in 17 of 36 participants (47%) and in 45 out of 184 cycles (24%), despite use of a lower dose of amifostine (740 mg/m²) compared to the other three trials. The hypotension was described as “grade 3” in two participants (three cycles) and grade 4 in three participants (four cycles), but considered to be of clinical relevance in only one participant. In the trial reported by Kemp et al. (Kemp 1996), amifostine was well tolerated; the principal adverse side effect was a transient decrease in blood pressure observed in 75 of 122 (62%) of participants during amifostine administration. In addition, emesis occurred in 96% of participants in the amifostine group relative to 88% of participants in the control group.

Details of other outcomes not specified in the protocol: Progression of disease (ovarian cancer) was similar in the amifostine and control groups after an average of 24 months of follow-up (Lorusso 2003). Amifostine did not compromise the anti-tumor effect of cisplatin in the treatment of ovarian cancer (Kemp 1996). However, amifostine also did not result in a higher dose intensity of cisplatin (Kemp 1996; Planting 1999).

Calcium and magnesium (Ca/Mg)

Primary outcome measure: No primary outcome measure was available in the single Ca/Mg study (Ishibashi 2010).

Secondary outcome measures

(1) *Nerve conduction measures of sensory response amplitudes:* SNAP amplitudes were not measured.

(2) *Clinical impairment on neurological examination using a validated scale:* None was included.

(3) *Functional activities of daily living:* None was included.

(4) *Information from toxicity rating scales:* The NCI Common Toxicity Criteria (NCI-CTC) and Debiopharm Neurotoxicity Scale (DEB-NTS) were used to assess the development and severity of neurotoxicity. According to the NCI-CTC criteria after six cycles of treatment, the incidence of Grade 1, 2, and 3 neurotoxicity were 100, 6, and 6% in the Ca/Mg group, respectively, and 94, 6, and 0% in the control group, there being no significant difference between groups. Similarly, according to the DEB-NTS criteria after six cycles of treatment, the incidence of Grade 1, 2, and 3 neurotoxicity was 100, 71, and 6% in the Ca/Mg group, respectively, and 94, 56, and 0% in the control group, there being no significant difference between groups, there again being no significant difference between groups. The authors did not comment on the acute neuropathy symptoms.

Adverse effects attributed to the study intervention: No adverse neurotoxicity was attributed to the Ca/Mg intervention.

Details of other outcomes not specified in the protocol: The authors reported in their final analyses that Ca/Mg infusions did not influence antitumor activity among participants.

However, their interim analyses had indicated that “the results of treatment were poor” in the Ca/Mg group than in the control group, resulting in discontinuation of subsequent enrolment.

Diethyldithiocarbamate (DDTC)

Primary outcome measure: No primary outcome measure was available in the single DDTC study (Gandara 1995).

Secondary outcome measures

(1) Nerve conduction measures of sensory response amplitudes: SNAP amplitudes were not measured.

(2) Clinical impairment on neurological examination using a validated scale: None was included.

(3) Functional activities of daily living: None was included.

(4) Information from toxicity rating scales: NCI toxicity rating scale showed 13 of 96 (13%) in the DDTC arm and 12 of 99 (12%) in the control group developed neuropathy (risk ratio of 1.12, 95% CI 0.54 to 2.32) (see Analysis 3.1).

Adverse effects attributed to the study intervention: Adverse effects were reported in all study participants with severe adverse events in 27 control group and 30 of DDTC arm. Twenty-two in the DDTC and nine in control group withdrew because of toxicity.

Details of other outcomes not specified in the protocol: None described.

Glutathione (GSH)

Primary outcome measure: QST was used as an outcome measure in only one study (Bogliun 1996). Although the manuscript does not state the site of recording the VPT, an increase in vibratory threshold by 2-3 fold, occurred in the GSH group versus 7-10 fold increase in the control group, 3 months after chemotherapy. One of the Cochrane authors (GC) who is a coauthor on this paper was able to retrieve the original information as follows. QST measured in cisplatin dosages of 50 and 75 mg/m² changed from baseline of 1.5 to 1.6 and 4.1 respectively in the GSH group, and changed from a baseline 1.6 and 1.7 to 8.3 and 9.4 respectively in the control group. No additional information was available.

Secondary outcome measures

(1) Nerve conduction measures of sensory response amplitudes: Sural SNAP amplitude decreased by a greater amount in control versus GSH arm (58% to 68% in controls versus 12% to 35% in the GSH arm) among participants receiving < 150 mg/m² or > 150 mg/m² respectively (Bogliun 1996). Similarly, Cascinu et al. (Cascinu 1995) documented a significant reduction of sural, median, and ulnar SNAP amplitudes in the control group versus GSH arm. At week 15, the sural SNAP decreased from 13.26 ± 4.1 µV to 7.92 ± 1.68 µV in the control arm and from 10.78 ± 5.84 µV to 8.95 ± 6.48 µV in the GSH arm. Median and ulnar SNAP amplitudes also reduced by significant amounts only in the control groups. In the oxaliplatin trial, the sural amplitude decreased in the placebo group from 10.9 to 7.2 µV but did not change in the GSH group (9.1 to 8.5 µV) after eight cycles of therapy (Cascinu 2002). No sensory nerve action potential amplitudes were measures in the other two studies (Schmidinger 2000; Smyth 1997).

(2) Clinical impairment on neurological examination using a validated scale: At three months post chemotherapy, five of 19 participants in the GSH group and eight of 16 in the control group changed in their neurological disability score (NDS) by > 12 points (risk ratio of 0.53, 95% CI 0.21 to 1.29) (see Analysis 4.1) (Bogliun 1996). In the same study, the neuropathy symptoms (NSS) developed in 14 of 19 participants in the GSH arm and all 16 participants in the control group (relative rate of 0.75, 95% CI 0.56 to 0.99) (see Analysis 8.1).

(3) Functional activities of daily living: Participants receiving received GSH reported an improvement in their quality of life (QOL). They also reported significantly less tingling in hands and feet and GSH allowed more cycles of cisplatin because of less toxicity (Smyth 1997).

(4) Information from toxicity rating scales: Four of 24 participants in GSH group developed neurotoxicity (three grade I and one grade II by WHO criteria) and 16 of 18 in control group (three grade I; ten grade II; two grade III and one grade IV) developed neuropathy by WHO neurotoxicity grade criteria (risk ratio of 0.19, 95% CI 0.08 to 0.47) (see Analysis 6.1) (Cascinu 1995). Grade 3 or 4 neurotoxicity by NCI-CTC was seen in 0 of 21 participants at eight weeks and 1 in 10 participants at 12 weeks in the GSH group and in 5 of 18 participants at eight weeks and 6 of 8 participants at twelve weeks in the control group (risk ratio of 0.13, 95% CI 0.02 to 0.89) (see Analysis 7.1) (Cascinu 2002). In one study, no change in WHO neurotoxicity was noted in either the GSH or the control group (Schmidinger 2000). After six cycles, neuropathy (CTC) was seen in 39% (24 grade 1 and 5 grade 2) in the GSH group and 49% in the control group (32 grade 1, 4 grade 2 and 2 grade 3) (Smyth 1997). Mean increase in HAD functional score was 0.8 in GSH arm and 2.5 in the control arm. In addition, 45 of 47 had better Rotterdam scores in GSH group. In another study identified in the 2010 update (Milla 2009), neurologic adverse effects were assessed using the neurosensory section of the Common Toxicity Criteria of the National Cancer Institute (NCI), version 3. At end of treatment, only moderate neurotoxicity was reported in the GSH arm (50% grade 1 and 50% grade 2), whereas in the placebo arm the neurotoxicity was more severe (69% grade 2 and 31% grade 3), a difference considered statistically significant (Mann-Whitney test; $P = 0.0037$). The combined results (Cascinu 2002 and Milla 2009) for participants displaying NCI grade 2 to 4 neurotoxicity after 12 cycles of oxaliplatin was 10 of 24 participants receiving GSH and 21 of 21 controls; $P = 0.0005$ (see Analysis 19.1).

Details of other outcomes not specified in the protocol: Oliguria occurred in 21 of 27 participants in CDDP alone and 10 of 27 participants in the CDDP with GSH group (risk ratio 0.48, 95% CI 0.28 to 0.81) (see Analysis 5.1) (Bogliun 1996). Participants in the GSH group also required less hemotransfusions and showed fewer incidences of thrombocytopenia and anemia than did participants in the control group (Cascinu 1995).

Adverse effects attributed to the study intervention: None described.

Details of other outcomes not specified in the protocol: None described.

Org 2766

Primary outcome measure: QST was used as an outcome measure in all four trials. Cisplatin neurotoxicity was measured by VPT recordings made from the second metacarpal bone of each hand (Hovestadt 1992; van Gerven 1994; van-der-Hoop 1990) or from the index finger and great toe (Roberts 1997). An increased threshold indicates worsening sensory performance. Three measurements of the VPT (in micrometers of skin

displacement) were recorded for each hand and the mean taken as the VPT for each side in one study (van-der-Hoop 1990). Two trials (Hovestadt 1992; van Gerven 1994) referred to the Gerritsen van der Hoop et al. (van-der-Hoop 1990) study in describing their methodology, but that study did not provide a clear description of the method actually used. The final study did not report details of the QST methodology used (Roberts 1997). Participants receiving treatment with Org 2766 1 mg/m² (n = 16) before and 24 hours after cisplatin administration showed significantly less increase in the VPT than did the 22 placebo treated participants (mean value after 4th cycle 0.50 versus 1.61, $P < 0.005$; mean value after 6th cycle 0.88 versus 5.87, $P < 0.005$) in the study by Gerritsen van der Hoop et al. (van-der-Hoop 1990). In the same study, the administration of Org 2766 at the dose of 0.25 mg/kg had no effect. In the study by Hovestadt et al. (Hovestadt 1992), only an exploratory, descriptive statistical analysis without formal tests for significance was performed, due to the low number of participants enrolled in the study (seven in the placebo group, five treated with Org 2766 at the dose of 0.25 mg/kg and six at the dose of 1 mg/kg). Mean values in placebo treated participants were higher than in the low- and high-dose Org 2766 treated participants one month after cisplatin treatment (mean 3.7 versus 2.9 versus 1.1, respectively), intermediate one to four months after treatment (8.1 versus 14.6 versus 2.5), and higher again after 4 to 12 and 12 to 24 months (4.8 versus 3.6 versus 2.0 and 2.9 versus 0.6 versus 0.8). However, the number of evaluable participants decreased markedly during the study and at the final evaluation only nine participants (no indication about treatment available) were assessed. VPT changes after 4th cycle and 3 to 5 months later was reported by van Gerven et al. (van Gerven 1994). Mean values obtained after 4th cycle (0.95 in placebo versus 0.45 in Org 2766 treated groups, number of participants 9 versus 6 respectively) and three to five months later (4.03 versus 1.85, number of participants 12 versus 8) were statistically compared with two different methods: the difference in slopes between Org 2766 and placebo treated groups was significant by ANOVA (P value = 0.04), but not by Wilcoxon's rank sum test ($P = 0.06$). In that study, VPTs became abnormal three to five months after treatment in 9 out of 12 placebo-treated patients and in 4 of the 8 patients treated with Org 2766 (risk ratio 0.67, 95% CI 0.31 to 1.43) (see Analysis 9.1). In the study by Roberts et al. (Roberts 1997) VPT was assessed separately for the index finger and for the great toe. After the blind was broken 174 participants (59 in the placebo, 52 in the 2mg/kg Org 2766 group, and 57 in the 4 mg/kg Org 2766 group) were evaluable. At each time point (i.e., at each cisplatin cycle up to six courses and monthly for three months after treatment withdrawal) no difference was observed between groups. The four Org 2799 studies all performed QST and evaluated our primary outcome measure, VPT. Three of the trials (Roberts 1997, van-der-Hoop 1990, and van Gerven 1994) measured VPT at the index finger or hand, and evaluated comparable doses of Org 2799 (1 mg or 2 mg). Based on comparison of the Org 2799 treatment and placebo groups at 3 to 5 months, the combined data from the three trials showed no significant group difference at the follow-up QST examination (-1.77 (95% CI -4.78 to 1.23) - random effects model) (see Analysis 10.1).

Secondary outcome measures

(1) Nerve conduction measures of sensory response amplitudes: This secondary outcome measure was not used in any of the selected trials.

(2) Clinical impairment on neurological examination using a validated scale: There was no use of a uniform or standardized neurological examination scale among the studies, but clinical scales were used that were based on descriptions of conventional neurological symptoms or signs. In one trial (van-der-Hoop 1990) neurological examination was based on a series of signs and symptoms evaluated after 4 and 6 chemotherapy courses, resulting in a "sum score." Using this score a difference was observed only for the high dose Org 2766 treatment at the evaluation performed after the 6th course versus the placebo treated

participants ($P = 0.03$). Two other trials used non validated neurological scales (Hovestadt 1992; van Gerven 1994) and no statistical comparison was performed. In one trial (Roberts 1997), it is stated that the neurological evaluation was used to assess the occurrence of inclusion/exclusion criteria, but no data are available about the severity. In this trial, repeated neurological examinations failed to demonstrate any significant difference between Org 2766 and placebo treated participants up to three months after cisplatin treatment withdrawal.

(3) Functional activities of daily living: This secondary outcome measure was not used in any of the selected trials.

(4) Information from toxicity rating scales: In one study (van Gerven 1994) it was reported that two participants in the placebo group and one in the Org 2766 group discontinued cisplatin treatment because of peripheral neurotoxicity ($P =$ not significant). No details about neurotoxicity-induced treatment withdrawal were reported in the other three trials.

Adverse effects attributed to the study intervention: No adverse effects were attributed to Org 2766 in any trial.

Details of other outcomes not specified in the protocol: Progression of disease (ovarian cancer) was similar in the Org 2766 and control groups after an average of 24 months of follow-up (Roberts 1997). Org 2766 did not compromise the anti-tumor effect of cisplatin in the treatment of ovarian cancer (van-der-Hoop 1990).

Oxycarbazepine (OXC)

Primary outcome measure: QST was not used as a primary outcome measure in the single OXC study available (Argyriou 2006a).

Secondary outcome measures

(1) Nerve conduction measures of sensory response amplitudes: This secondary outcome measure was reported for sural, superficial peroneal, and ulnar SNAP amplitudes, of which a modest but significant decline in amplitude pre- to post treatment was reported for the control group relative to the OXC group for the sural (14.5 ± 6.1 to $8.3 \pm 6.1 \mu\text{v}$ versus 13 ± 6.8 to $11.5 \pm 7.1 \mu\text{v}$) (see Analysis 16.1) and superficial peroneal (9.2 ± 3.2 to $6.8 \pm 4.8 \mu\text{v}$ versus 9.3 ± 4.0 to $8.8 \pm 4.4 \mu\text{v}$) amplitudes (see Analysis 16.2 for post treatment comparison) but not for the ulnar SNAP (see Analysis 16.3 for post treatment comparison) or peroneal motor amplitudes. However, group comparisons of SNAP amplitudes at post-treatment (at 6 months after 24 cycles) showed no significant differences.

(2) Clinical impairment on neurological examination using a validated scale: Based on a neurologic symptom score (NSS) and the neurologic disability score (NDS), the incidence of oxaliplatin-induced neuropathy was decreased among those who completed the trial in the OXC group relative to the control group (5 of 16 versus 12 of 16) (see Analysis 15.1), and the between-group comparisons of the NSS (0.6 ± 0.9 versus 1.5 ± 1.3) and NDS (5 ± 8.2 versus 20.0 ± 23.1) differed significantly, both favoring the OXC group. Also, the severity of oxaliplatin-induced neuropathy was significantly lower in the OXC group versus controls, based on the total neuropathy scores (see Analysis 15.2). None of the participants receiving OXC reported negative sensory symptoms versus 3 controls; 5 participants receiving OXC reported positive sensory symptoms versus 12 controls.

(3) Functional activities of daily living: This secondary outcome measure was not used in the selected trial.

(4) Information from toxicity rating scales: None described

Adverse effects attributed to the study intervention: Adverse chemotherapy effects described but none was attributed to OXC (similar frequency in both groups)

Details of other outcomes not specified in the protocol: None reported.

Vitamin E

Primary outcome measure: QST was not performed in the study identified in the initial (Pace 2003) or 2010 update (Argyriou 2006) searches.

Secondary outcome measures

(1) Nerve conduction measures of sensory response amplitudes: In the study reported by Pace et al. (Pace 2003), after 6 cycles of treatment, 4 of 13 patients in the vitamin E group had at least one abnormal finding among the median sensory or sural sensory amplitude, whereas 11 of 14 patients in the control group had at least one abnormal amplitude (risk ratio 0.39, 95% CI 0.17 to 0.93) (see Analysis 12.1). Nerve conduction measures of sensory response amplitudes showed that the median SNAP amplitudes were reduced by a greater degree in those without vitamin E than those taking vitamin E (without vitamin E group: baseline $14.5 \pm 8.5 \mu\text{v}$; 6 months later $13.6 \pm 9.2 \mu\text{v}$; Vitamin E group: baseline $15.5 \pm 6.3 \mu\text{v}$; 6 months later $13.7 \pm 5.5 \mu\text{v}$). However, the small differences in the sural amplitudes observed after 6 cycles of treatment did not differ significantly between the Vitamin E and placebo groups ($0.10 \mu\text{v}$, 95% CI -5.57 to $5.77 \mu\text{v}$) (see Analysis 11.1). In the second vitamin E trial (Argyriou 2006), after 6 cycles of treatment and 3 months after treatment ended, all SNAP amplitudes (sural, superficial peroneal, and ulnar) had deteriorated, although the change from baseline was significantly less in the vitamin E group relative to controls. In contrast, the peroneal and ulnar motor amplitudes and conduction velocities showed no significant group differences in terms of change from baseline (see Analysis 11.2 and Analysis 11.3). However, group comparisons of the SNAP amplitudes at post-treatment (at end of treatment and 23 months later) showed no significant differences, although the comparison of the superficial peroneal SNAP amplitude for the vitamin E and control groups was borderline-significant (8.5 ± 6.6 versus $4.9 \pm 3.6 \mu\text{v}$; $P = 0.07$) showing slightly better performance for the vitamin E group. When the sural nerve results at end of treatment were combined for the two studies, no significant treat effect existed (see Analysis 11.1).

(2) Clinical impairment on neurological examination using a validated scale: Although clinical impairment on neurological examination was measured in both selected trials (Pace 2003 and Argyriou 2006), neither trial used a validated scale. Argyriou et al. (Argyriou 2006) reported that the incidence of clinical neuropathy was less in the vitamin E group was less than in the control group among participants completing the study (3 of 14 versus 11 of 16; $P = 0.03$) (see Analysis 17.2). Similar results were reported for the intention-to-treat analysis (see Analysis 17.1). The severity of clinical neuropathy, as judged by the means of a modified peripheral neuropathy score at trial end, also showed a significant difference favoring the vitamin E group (4.99 ± 1.33 versus 10.47 ± 10.62 , $P = 0.04$) (see Analysis 18.1).

(3) Functional activities of daily living: The authors (Pace 2003 and Argyriou 2006) did not measure any functional activities of daily living and did not provide any information on standardized toxicity rating scales

(4) Information from toxicity rating scales: In the study by Pace et al. (Pace 2003), the incidence of neurotoxicity, measured by modified version of total neuropathy score, was

significantly lower in the group with vitamin E supplementation (4 of 13) compared with the group without vitamin E (12 of 14; risk ratio of developing symptoms or signs of neurotoxicity was 0.36, 95% CI 0.15 to 0.83) (see Analysis 13.1). In addition, the severity of neuropathy, measured with neurotoxicity scores was higher (worse) in participants without vitamin E supplementation compared to those with vitamin E (4.7 versus 2.0, $P < 0.01$). Argyriou et al. (Argyriou 2006), using a measure presumably derived from a modified Peripheral Neuropathy (PNP) score, reported results similar to those of Pace et al., including mean PNP scores in the vitamin E group versus controls of 4.99 ± 1.33 and 10.47 ± 10.62 , respectively ($P = 0.023$). The combined results from these two studies identified neurotoxicity after completion of chemotherapy in 9 of 29 participants receiving vitamin E versus 25 of 33 controls ($P = 0.002$) (see Analysis 13.1).

Adverse effects attributed to the study intervention: No information was provided pertaining to the adverse effects attributed to the study (interventions) treatment (Pace 2003). Overall adverse effects experienced were judged unlikely to be due to vitamin E supplementation (Argyriou 2006).

Details of other outcomes not specified in the protocol: None described.

Discussion

Acetylcysteine (N-acetylcysteine, NAC)

The single eligible study evaluating the use of NAC against the neurotoxicity of oxaliplatin was described as a pilot study and included only a small number of participants (5 receiving NAC and 9 controls). In addition, uncertainty about the randomization methods and presence of blinding (participants or investigators), report only of subjective toxicity scales, and inclusion of nerve conduction results from the NAC group but not the control group are issues that limit interpretation of the preliminary study results.

Amifostine

The few eligible studies evaluating the use of amifostine as a neuroprotective agent against the neurotoxicity of cisplatin and other chemotherapy agents are inconclusive in demonstrating efficacy. Although the studies were generally well done, patient masking was unclear, perhaps because amifostine was given intravenously in conjunction with interval chemotherapy and felt to be of little interest to the recipient. The authors of one study acknowledged that the trial was not conceived as a double-blind study, but that the physicians assessing non-hematological toxicity usually were not the same physicians involved in administering treatment and they therefore could not be influenced by the evaluation of symptoms and signs associated with chemotherapy (Lorusso 2003). It is unknown whether this belief about the low likelihood of inadvertent influence on judgment is correct. Paclitaxel was used together with carboplatin in two of the amifostine trials which were included (Kanat 2003; Lorusso 2003).

The trial reported by Planting et al. (Planting 1999) was the single study that included QST, our primary outcome measure, among their assessment instruments. That trial showed a favorable outcome in terms of amifostine neuroprotection, but the subclinical result was based on only 14 participants in the amifostine group and 20 participants in the control group and the results were not particularly robust, showing statistical but unclear clinical significance. Among the secondary outcome measures we selected, the only other quantitative measure used in any of the four studies was related to evaluation of peripheral nerve electrophysiology. A single study (Kanat 2003) utilized electrophysiological measures, recording SNAP amplitudes from two upper extremity sensory nerves and one

lower extremity sensory nerve at baseline and after completing chemotherapy. This study, which also included a relatively small number of participants (19 participants in each study arm), found that the quantitative measures of large fibre sensory axons failed to identify evidence of significant amifostine neuroprotection. Unfortunately, the study also showed an unexpected and almost implausible low level of neurotoxicity among the control participants who received carboplatin and paclitaxel but not amifostine, rendering the amifostine efficacy result uninterpretable.

Despite the lack of quantitative measures showing amifostine efficacy, the authors of all four trials concluded that pre-treatment with amifostine reduced, prevented, or at least exerted some protection from the cumulative neurotoxicity associated with cisplatin or carboplatin and paclitaxel. This conclusion reflected the results obtained from the various neurological examination scales or neurotoxicity scales. For the most part, the scales utilized were of unknown sensitivity or specificity, and the clinical relevance of the results uncertain. For example, it is unclear whether any of the sensory symptoms or signs resulted in substantial functional impairment or persisted. Some of the neurotoxicity results were reported in terms of each evaluation, rather than for each participant, suggesting fluctuation during the trial. Such fluctuation suggests inclusion of non-specific symptoms, as opposed to persistent distal predominant and symmetrical sensory symptoms and signs characteristic of most toxic neuropathies. One exception is the functional activities of daily living scale reported by Kanat et al. (Kanat 2003). Although based on a small number of participants (19 participants in each study arm), the results of this sensorimotor neurotoxicity score suggested a small but statistically significant decrease in the activities of daily living in 2 of 19 participants in the amifostine group compared to 9 of 19 participants in the control group (relative rate of 0.22, 95% CI 0.6 to 0.90). Another exception reflected the use of the NCI neurologic toxicity rating among 242 participants with ovarian cancer treated with cisplatin and cyclophosphamide (Kemp 1996). The significant decrease in the NCI rating among participants pre-treated with amifostine compared to control participants was an impressive finding, despite the lack of QST or electrophysiological evaluations. The limited availability of clinical trials utilizing conventional QST and nerve conduction study measures of peripheral nerve function is disappointing, at least in part because of the relative simplicity of the peripheral nervous system evaluation relative to other neurologic functions, such as behavior.

In terms of direct chemotherapy relevance, the expectation that reduced neurotoxicity would result in increased dosing was not realized in any of the trials reviewed. The expectation of the beneficial result of increased dosing is based on recognition that neurotoxicity is the primary dose limiting adverse effect attributed to cisplatin. In conclusion, although the results of these few trials suggest the possibility of potential amifostine neuroprotection, they appear to be of small magnitude or not convincingly positive in favor of amifostine neuroprotection against cisplatin and other chemotherapy agents, and the overall efficacy results are inconclusive.

Calcium and magnesium (Ca/Mg)

The single study of Ca/Mg infusions as a chemoprotective agent against oxaliplatin neurotoxicity had no measures of neurotoxicity other than subjective NCI and DEB neurotoxicity grading criteria (Ishibashi 2010). Enrolment in the study was terminated prematurely, due to treatment results that were poorer in the Ca/Mg group than in the control group according to their interim analyses, results not confirmed in the final analyses. The early discontinuation resulted in a small sample size and insufficient data to determine if Ca/Mg infusions had neuroprotective potential, although the available data did not suggest evidence of any beneficial effect.

Diethyldithiocarbamate (DDTC)

The single study of DDTC as a neuroprotective agent suffers from having no measures of neurotoxicity other than subjective reporting (NCI). To gain full appreciation of the magnitude of the difference in the two arms, one should probably add those withdrawn for toxicity, to patient request, and adverse experience (Gandara 1995).

Glutathione (GSH)

Overall, five out of six studies reported a significant protective effect of GSH. All measures of peripheral neuropathy favored the GSH group, including the measure of VPT (one study), sural SNAP amplitudes (three studies) and improvement in functional measures or neurotoxicity rating scales (five studies). Even though the overall effect of GSH appears to be protective, the variable dosages used with different malignancies and different combination of chemotherapy, high drop out rate, predominant reliance on subjective measures, limited statistical analyses, and lack of long-term follow-up, make the overall effect of GSH difficult to judge.

Org 2766

Overall, the few eligible studies evaluating the use of Org 2766 as a neuroprotective agent against the neurotoxicity of cisplatin are inconclusive in demonstrating efficacy. A major concern is that the total number of patients enrolled in the studies is rather low (188 Org 2766 treated and 123 control participants) and, moreover, participants are not homogeneously distributed among the four trials, since one of them (Roberts 1997) included 68% of the Org 2766 treated and 54% of the control participants. All the trials included QST, our primary outcome measure, among their assessment instruments, while evaluation of peripheral nerve electrophysiology and determination of any effect of daily living activities were not reported in any study. Neurological examination was based on non-validated scales in all the four trials.

The first study suggesting a protective effect of Org 2766 (van-der-Hoop 1990) is based on an inadequate statistical analysis. In fact, analysis was performed after six cycles of cisplatin on only 28 participants out of the 55 admitted to the study, while the others were not eligible or had not yet received the planned chemotherapy cycles. Intermediate analysis (i.e. after four cycles of cisplatin) was performed on 39 participants. The authors of the second study (Hovestadt 1992) admitted that the number of participants was too low to allow a reliable formal statistical analysis. The third study was the only one performed mostly on males (22 males versus 1 female). Two different methods of statistical analysis were used by the authors (van Gerven 1994) and the results were conflicting. The largest study (Roberts 1997) had adequate subject, outcome assessor and observer blinding and also the statistical analysis was adequate. Instead of providing evidence of protection induced by Org 2766, the authors suggested that high doses of the compound might even increase the rate of change and degree of neuropathy induced by cisplatin (P value > 0.05).

In conclusion, although the results of the first trial (van-der-Hoop 1990) suggested the possibility of potential Org 2766 neuroprotection, they appear to be of small magnitude or not convincingly positive in favor of Org 2766 neuroprotection, particularly in view of the results reported in the most recent trial (Roberts 1997). Furthermore, the combined data from the three trials using the same measure showed no significant group difference at the follow-up QST examination (0.06, 95% CI -0.53 to 0.65). The overall efficacy results are negative.

Oxycarbazepine (OXC)

The only study evaluating the efficacy of OXY for prophylaxis against oxaliplatin-induced neuropathy reported a favorable effect (Argyriou 2006a). The results were based on an open label evaluation (randomized but not placebo controlled), a small sample size, and without quantitative sensory testing as a primary outcome measure. However, validated clinical instruments (NSS and NDS) and appropriate neurophysiological measures were incorporated and showed several significant group differences, all favoring the OXC group. The significant nerve conduction results involved a change in the baseline to six month recordings for the lower extremity SNAP amplitude measures (sural and superficial peroneal), but not the ulnar sensory or peroneal motor measures, results consistent with those expected to represent the most sensitive indicators of an oxaliplatin-induced neuropathy. Comparisons of the mean SNAP amplitudes for the treatment versus control groups at post-treatment (six month recordings after 24 cycles) showed no significant differences in any of the SNAP amplitudes, however. Although the significant neurophysiological group differences based on the change from baseline to six month records were modest and of uncertain clinical importance, the overall results support further investigation of OXC in a larger placebo controlled randomized trial.

Vitamin E

Although the results involving vitamin E as a neuroprotective agent are encouraging, methodology issues, small size of the study, multiple chemotherapeutic regimens, lack of blinding, and lack of primary outcome measures make this study less than convincing. The changes noted in median SNAP but not the in sural SNAP amplitudes and use of a non-validated toxicity measure suggest that additional more definitive studies are needed.

Comment

The quality and characteristics of the trials reviewed were quite variable, and included different measures of neuropathy (qualitative and subjective), different durations of follow-up, and different analyses. The duration of follow-up must be sufficient to identify cisplatin-induced sensory nerve deterioration, and therefore should extend beyond the last cisplatin treatment. How long after the last treatment is open to debate, as all toxic neuropathies demonstrate some progression after exposure ceases, and patients with cisplatin-induced neuropathy can show improvement (depending on the initial severity) after cisplatin is discontinued. We included all evaluations performed zero to six months after the last treatment, selecting the evaluation closest to three months after treatment to the extent possible. We believe that a two to three month interval after treatment is completed is biologically reasonable. In all, 16 trials were included in our initial review and 11 trials in our 2010 review. The combined trials involved nine separate, unrelated potential neuroprotective agents and included many disparate measures of neuropathy, resulting in insufficient data for any one measure to combine the results. Based on our review, we feel that the evaluation of agents intended to prevent cisplatin-induced sensory neuropathy should include among the primary measures tests of QST at the index finger and great toe and nerve conduction study evaluation of SNAP amplitudes in the median sensory and sural nerves. Before performing our review, considerable consideration was given to two measures (QST or NCS) competing for the primary endpoint. We selected QST as the primary endpoint, in part, because it had been used in several prominent trials. While QST is an excellent quantitative measure of the endpoint of interest (sensation), the SNAP amplitude has the advantage of providing information about the actual cisplatin target, the peripheral sensory nerve, independent of patient cooperation or motivation. Sufficient information exists about both measures to perform power calculations to determine the number of subjects required to detect a meaningful group difference. A difficulty we experienced in performing our review related to the limited data available, even when QST

or SNAP amplitude recordings were performed. Most studies provided only descriptive statistics (e.g., mean, SD) reflecting the baseline examination and the follow-up examination for treatment and control groups, without information about change (mean, SD) between baseline and follow-up examinations. Inclusion of the latter facilitates comparisons with subsequent studies.

Authors' Conclusions

Implications for practice

There is no high quality evidence that any agent has been demonstrated as neuroprotective against cisplatin-induced neuropathy.

Implications for research

There is a continued need for randomized controlled clinical trials, using objective measures of neuropathy, utilizing appropriate masking of subjects and examiners, and including adequate numbers of participants to evaluate the efficacy of neuroprotective agents

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Sources of Support

Internal sources

- None, Not specified.

External sources

- None, Not specified.

Appendix 1: MEDLINE (OvidSP) search strategy

1. randomised controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. (animals not (animals and humans)).sh.
11. 9 not 10
12. cisplatin/ae, tu, to

13. cisplatin.tw.
14. cis-diamminedichloroplatinum.tw.
15. platinum compounds.tw. or platinum compounds/ae, to, tu
16. exp organoplatinum compounds/ae, to, tu
17. (oxaliplatin or carboplatin).tw.
18. or/12-17
19. exp peripheral nervous system diseases/ci, pc
20. exp central nervous system diseases/ci, pc
21. (neuropath\$ or neuro\$ or nerv\$).tw.
22. or/19-21
23. 18 and 22
24. exp neuroprotective agents/
25. chemoprotect\$.mp.
26. Protective Agents/
27. neuroprotective agents/
28. (protect\$ or neuroprotect\$).tw.
29. (ORG2766 or ORG 2766).tw.
30. Adrenocorticotrophic Hormone/
31. (acth or corticotropin or corticotrophin or adrenocorticotropin or adrenocorticotrophin).tw.
32. glutathione/or glutathione.tw.
33. amifostine.tw. or amifostine/
34. exp nerve growth factors/
35. (nerve adj3 growth adj3 factor\$).tw.
36. neurotrophin 3.tw.
37. exp antidotes/
38. antidote\$.tw.
39. vitamin E.tw. or vitamin E/
40. (alc or acetyl l carnitine).tw.
41. Acetylcarnitine/
42. or/24-41
43. 11 and 18 and 22 and 42
44. random\$.tw.
45. 43 and 44

Appendix 2: EMBASE (OvidSP) search strategy

1. crossover-procedure/
2. double-blind procedure/
3. randomized controlled trial/
4. single-blind procedure/
5. (random\$ or factorial\$ or crossover\$ or cross over\$ or cross-over\$ or placebo\$ or (doubl\$ adj blind\$) or (singl\$ adj blind\$) or assign\$ or allocat\$ or volunteer\$).tw.
6. or/1-5
7. human/
8. 6and 7
9. nonhuman/or human/
10. 6 not 9
11. 8 or 10
12. CISPLATIN/ae, to [Adverse Drug Reaction, Drug Toxicity]
13. cisplatin.tw.
14. cis-diamminedichloroplatinum.mp.
15. Platinum Derivative/ae, to [Adverse Drug Reaction, Drug Toxicity]
16. (platinum compound or platinum derivative).mp.
17. Platinum Complex/ae, to [Adverse Drug Reaction, Drug Toxicity]
18. oxaliplatin.tw. or OXALIPLATIN/
19. carboplatin.tw. or CARBOPLATIN/
20. or/12-19
21. exp Peripheral Neuropathy/
22. (neuropath\$ or neuro\$ or nerv\$).mp.
23. 21 or 22
24. 20 and 23
25. Neuroprotective Agent/
26. Neuroprotection/
27. (chemoprotect\$ or neuroprotect\$ or protect\$).mp.
28. (ORG 2766 or ORG2766).mp.
29. CORTICOTROPIN/
30. (acth or corticotropin or corticotrophin or adrenocorticotropin or adrenocorticotrophin).mp.
31. GLUTATHIONE/or Glutathione.tw.
32. amifostine.tw. or AMIFOSTINE/
33. Nerve Growth Factor/

34. (nerve adj growth adj factor).tw.
35. neurotrophin 3.tw. or Neurotrophin 3/
36. antidote\$.tw. or Antidote/
37. vitamin E.tw. or Alpha Tocopherol/
38. (ALC or acetly l carnitine).tw.
39. or/25-38
40. 11 and 20 and 24 and 39

Appendix 3: CINAHL (EBSCOhost) search strategy

S45 S18 and S26 and S30 and S44

S44 S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43

S43 acetyl l carnitine or alc

S42 (MH "Carnitine")

S41 ("vitamin e") or (MH "Vitamin E")

S40 ("antidotes") or (MH "Antidotes")

S39 neurotrophin 3

S38 growth and factor

S37 ("amifostine") or (MH "Amifostine")

S36 (glutathione) or (MH "Glutathione")

S35 acth or corticotropin or corticotrophin or adrenocorticotropin or adrenocorticotrophin

S34 (MH "Corticotropin-Releasing Hormone") or (MH "Adrenocorticotrophic Hormone")

S33 ORG 2766 or ORG2766

S32 chemoprotect* or neuroprotect* or protect*

S31 (MH "Neuroprotective Agents+")

S30 S27 or S28 or S29

S29 (MH "Peripheral Nervous System Diseases/CI/PC")

S28 (MH "Central Nervous System Diseases+/CI/PC")

S27 neuropath* or neuro* or nerv*

S26 S19 or S20 or S21 or S22 or S23 or S24 or S25

S25 (MH "Carboplatin")

S24 oxaliplatin or carboplatin

S23 ((platinum or organoplatunum) and compound*)

S22 (MH "Platinum/AE/TU")

S21 cis-diaminedichloroplatinum

S20 TI cisplatin or AB cisplatin

S19 (MH "Cisplatin/AE/PO/TU")

S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17

S17 ABAB design*

S16 TI random* or AB random*

S15 (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial or sham? or dummy))

S14 (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic)) and (TI (trial*) or AB (trial*))

S13 (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or systematic review*))

S12 (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind* or mask*))

S11 PT ("clinical trial" or "systematic review")

S10 (MH "Factorial Design")

S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies")

S8 (MH "Meta Analysis")

S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison")

S6 (MH "Quasi-Experimental Studies")

S5 (MH "Placebos")

S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies")

S3 (MH "Clinical Trials+")

S2 (MH "Crossover Design")

S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample")

Appendix 4: LILACS search strategy

((Mh CISPLATIN OR cisplatin OR cis-diamminedichloroplatinum OR platinum and compounds OR Mh platinum compounds OR Mh organoplatinum compounds OR oxaliplatin OR carboplatin) AND (Mh peripheral nervous system diseases OR neuropath\$ OR neuro\$ OR nerv\$ OR Mh central nervous system diseases)) [Words] and ((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535\$ OR (Tw clin\$ AND (Tw trial\$ OR Tw ensa\$ OR Tw estud\$ OR Tw experim\$ OR Tw investiga\$)) OR ((Tw singl\$ OR Tw simple\$ OR Tw doubl\$ OR Tw doble\$ OR Tw duplo\$ OR Tw trebl\$ OR Tw tripl\$) AND (Tw blind\$ OR Tw cego\$ OR Tw ciego\$ OR Tw mask\$ OR Tw mascar\$)) OR Mh placebos OR Tw placebo\$ OR (Tw random\$ OR Tw randon\$ OR Tw casual\$ OR Tw acaso\$ OR Tw azar OR Tw aleator\$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative

study OR Ex E05.337\$ OR Mh follow-up studies OR Mh prospective studies OR Tw control\$ OR Tw prospectiv\$ OR Tw volunt\$ OR Tw volunteer\$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Words]

Appendix 5: Cochrane Central Register of Controlled Trials search strategy

#1(cisplatin OR cis-diaminedichloroplatinum OR platinum OR organoplatinum OR oxaliplatin OR carboplatin)
 #2(therap* OR adverse OR toxic* OR neurotoxic*)
 #3(#1 AND #2)
 #4(neuroprotect* OR chemoprotect* OR protect* OR org2766 OR corticotrop* OR glutathione OR amifostine OR (growth NEXT factor*) OR neurotrophin3 OR neurotrophin3 OR antidote* OR (vitamin NEXT E))
 #5MeSH descriptor Acetylcarnitine, this term only
 #6(acetyl l carnitine) or alc
 #7(#4 OR #5 OR #6)
 #8(neuropath* OR nerv* OR neurotox* OR neurol*)
 #9MeSH descriptor Peripheral Nervous System Diseases, this term only
 #10MeSH descriptor Peripheral Nerves, this term only
 #11(#8 OR #9 OR #10)
 #12(#3 AND #7 AND #11)

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Plain Language Summary

Interventions for preventing neuropathy caused by cisplatin and other tumor inhibiting platinum drugs

Cisplatin and other related platinum drugs used to treat solid tumors are toxic to the nervous system. Most people who complete a full course of cisplatin chemotherapy develop a sensory neuropathy. Symptoms can include tingling in the extremities and numbness. The neuropathy may only partially recover or not recover at all. To try to reduce the toxicity of platinum drugs, neuroprotective therapies have been sought. These include acetylcysteine, acetyl-L-carnitine, amifostine, calcium and magnesium, growth factors, glutathione, Org 2766, oxcarbazepine, and vitamin E. The initial review identified 16 randomized controlled trials of five different potential neuroprotective therapies. The 2010 update identified an additional 5 randomized controlled trials, which described three potential chemoprotective therapies not included in the 2006 review. Although the trials included a total of 1,537 participants, meta-analysis was possible for only a small number of measures in very few trials. The data from the trials were insufficient to conclude that any of the neuroprotective agents tested prevent or limit the neurotoxicity of platinum drugs.

	Adequate sequence generation?	Allocation concealment?	Blinding? (subject)	Blinding? (observer)	Blinding? (All outcomes)	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Argyriou 2006	?	+	+	+	?	+	+	+
Argyriou 2006a	?	?	+	+	?	+	+	?
Bogliun 1996	?	?	+	+	?	+	+	+
Cascinu 1995	+	+	+	+	?	?	?	?
Cascinu 2002	+	+	+	+	+	?	?	+
Gandara 1995	?	?	+	+	?	?	?	+
Hovestadt 1992	?	?	+	+	?	?	?	+
Ishibashi 2010	?	+	+	+	+	?	?	?
Kanat 2003	?	?	+	?	?	?	?	+
Kemp 1996	?	?	+	+	?	?	+	+
Lin 2006	?	?	?	?	?	?	?	?
Lorusso 2003	+	+	+	?	?	?	?	+
Milla 2009	?	?	?	?	?	+	?	?
Pace 2003	?	?	+	+	?	?	?	+
Planting 1999	?	?	?	?	?	+	?	+
Roberts 1997	?	?	+	?	?	+	+	+
Schmidinger 2000	?	?	?	?	?	+	+	+
Smyth 1997	+	+	?	?	?	?	?	+
van Gerven 1994	?	?	?	?	?	?	+	+
van-der-Hoop 1990	?	+	+	+	+	+	+	+

Figure 1.
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Characteristics of Studies: Characteristics of included studies [ordered by study ID]

Argyriou 2006		
Methods	Prospective, randomized, open label with blind assessment	
Participants	30 participants with variety of cancers scheduled to receive cisplatin-based regimens plus other chemotherapy agents (including 5 who received docetaxel); 14 participants received Vitamin E supplementation and 16 participants served as controls	
Interventions	Vitamin E 600 mg/d during and for 3 months after completion of chemotherapy treatment	
Outcomes	1. Sural SNAP amplitude showed a significant decline in control group relative to Vit E group. 2. Superficial peroneal SNAP amplitude showed a significant decline in control group relative to Vit E group. 3. Ulnar SNAP amplitude showed a significant decline in control group relative to Vit E group. 4. The overall incidence of peripheral neuropathy differed significantly (5/16 vitamin E vs. 13/19 no vitamin E)	
Notes	Authors concluded that 1. vitamin E was well tolerated and effectively protected against cisplatin neurotoxicity, a result supported by electrophysiology, although 2.due to the lack of a placebo group, unable to rule-out the possibility that bias contaminated participant self-reported information	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized but method of the "simple" randomization method not described
Allocation concealment?	Low risk	Opaque, sealed envelopes containing random numbers (I or II)
Blinding? subject	High risk	Not done, as subject given vitamin E or no vitamin E
Blinding? observer	Low risk	Both neurologists were blinded to group assignment until study completion
Blinding? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Low risk	Evaluated neurotoxicity on all subjects completing trial and efficacy using intention-to-treat analyses
Free of selective reporting?	Low risk	Yes, as above
Free of other bias?	Low risk	No evidence of other bias identified
Argyriou 2006a		
Methods	Prospective, randomized, open label with blind assessment	
Participants	Initially participants with colon cancer scheduled to receive FOLFOX-4, which included oxaliplatin 85 mg/m ² every two weeks for 12 courses; 20 participants were randomized to treatment with oxcarbazepine and 20 to no treatment (16 participants in each group completed the study for n = 32 total)	
Interventions	Oxcarbazepine, initiated at 150 mg/d and titrated over 4 weeks to 600 mg twice daily and maintained for 20 weeks)	
Outcomes	1. Sural SNAP amplitude showed a significant decline in control group relative to the oxcarbazepine group. 2. Superficial peroneal SNAP amplitude showed a significant decline in control group relative to oxcarbazepine group. 3. Ulnar SNAP amplitude showed no significant group difference. 4. The overall incidence of peripheral neuropathy differed significantly (9/20 oxcarbazepine versus 16/20 no treatment). 5. The severity of neuropathy (total neuropathy score) significantly favored the oxcarbazepine group	
Notes	Authors concluded that oxcarbazepine might be able to protect against oxaliplatin-induced neuropathy. They acknowledged that the small sample size and the lack of a placebo group were limitations of the study design, but larger placebo-controlled trials were warranted	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized method not specifically described, other than 1:1 ratio
Allocation concealment?	Unclear risk	Described as "concealed," known only to the randomization coordinator

Blinding? subject	High risk	"Open label" trial
Blinding? observer	Low risk	The evaluators and the senior oncologist were blinded to subject group assignment
Blinding? All outcomes	Unclear risk	Presumably but not specifically described
Incomplete outcome data addressed? All outcomes	Low risk	Evaluated neurotoxicity on all subjects completing trial and efficacy using intention-to-treat analyses
Free of selective reporting?	Low risk	Yes, as above
Free of other bias?	Unclear risk	No evidence of other bias identified

Bogliun 1996

Methods	Prospective, randomized, placebo controlled	
Participants	54 participants with ovarian cancer treated with cisplatin (50 mg/m ² and 75 mg/m ² × 3 weeks); 27 participants received GSH and 27 participants served as controls	
Interventions	GSH 2.5 G before cisplatin	
Outcomes	1. VPT: 2 to 3 fold increase in GSH arm and 7 to 10 fold increase in control 2. Sural amplitude decreased by 68 to 68%(GSH) versus 12 to 35%(control) 3.NIS 5/19 versus 8/16 changed > 12 points 4. NSS 14/19 versus 16/16	
Notes	1. No statistics used because of small numbers 2. Trend towards less PN with GSH in all measures. The authors concluded that, despite the small numbers and lack of statistical analyses, neuroprotection was not complete but there was a trend toward less severe toxicity after co-treatment with GSH	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Unclear
Blinding? subject	High risk	randomized but not blinded
Blinding? observer	High risk	Same
Blinding? All outcomes	Low risk	The analyses of data were performed without knowledge of treatment
Incomplete outcome data addressed? All outcomes	Unclear risk	No formal statistical analyses
Free of selective reporting?	Low risk	Few subjects lost to follow-up
Free of other bias?	Low risk	None identified

Cascinu 1995

Methods	Prospective, randomized, placebo controlled	
Participants	50 participants with ovarian cancer treated with cisplatin (40 mg/m ² every week × 9 weeks); 25 participants received GSH and 25 participants served as controls	
Interventions	GSH 1.5 G/m ² before cisplatin	
Outcomes	1. Sural SNAP significant change in control group. 2. Ulnar SNAP- significant change in control group. 3. Median SNAP- significant change in control group. 4. 0 at 9 weeks versus 66% in control group by WHO and 4/24 at 15 weeks versus 16/18 in control group	
Notes	Long-term follow-up unclear. The authors believed that the results established GSH as a promising and partially effective agent for the prevention of CDDP-induced and oxaliplatin-induced neurotoxicity	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Random, computer-generated
Allocation concealment?	Low risk	Adequate, concealed envelopes
Blinding? subject	Low risk	Placebo controlled

Blinding? observer	Low risk	The same blinded evaluator examined all subjects
Blinding? All outcomes	Unclear risk	Not specifically described
Incomplete outcome data addressed? All outcomes	Unclear risk	Based on assessable subjects
Free of selective reporting?	Unclear risk	Same
Free of other bias?	Unclear risk	None identified

Cascinu 2002

Methods	Prospective, randomized, placebo controlled	
Participants	52 participants with colorectal cancer treated with oxaliplatin (100 mg/m ² × 2 every 2 weeks); 26 participants received GSH and 26 placebo-treated participants served as controls	
Interventions	GSH 1.5 G/m ² or placebo before oxaliplatin	
Outcomes	Oxaliplatin 100 mg/m ² × 2 every 2 weeks GSH 1.5 G/m ² before oxaliplatin or normal saline as placebo	
Notes	GSH reduces symptoms and signs of neuropathy significantly. Sural amplitude and latency- partially protective. The authors believed that the results established GSH as a promising and partially effective agent for the prevention of CDDP-induced and oxaliplatin-induced neurotoxicity	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Used cards from a computer-generated list in sealed envelopes
Allocation concealment?	Low risk	Same
Blinding? subject	Low risk	Double blinded RCT
Blinding? observer	Low risk	Same
Blinding? All outcomes	Low risk	Yes
Incomplete outcome data addressed? All outcomes	Unclear risk	Analyses based on evaluable subjects
Free of selective reporting?	Unclear risk	Same
Free of other bias?	Low risk	None identified

Gandara 1995

Methods	Prospective, randomized, placebo controlled	
Participants	214 participants with ovarian cancer, SCLC, or NSCLC treated with cisplatin (100 mg/m ² every 4 weeks × 6); 106 participants received DDTC and 108 participants received placebo. Data were available for n = 195 patients from the combined lung and ovarian cancer populations (PB, 99 patients; DDTC, 96 patients)	
Interventions	DDTC 1.6 G/m ² 15 min before cisplatin	
Outcomes	NCI toxicity rating scale showed 13 of 96 (13%) in the DDTC arm and 12 of 99 (12%) in the control group developed neuropathy (P = not significant)	
Notes	Adverse effects were reported in all study participants with severe adverse events in 27 control group and 30 of DDTC arm. The authors concluded that DDTC is not effective against protecting cisplatin induced peripheral neuropathy	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Presumably, but not described
Blinding? subject	Low risk	Placebo controlled
Blinding? observer	Low risk	Described as blinded, including a blinded interim safety analysis

Blinding? All outcomes	Low risk	Independent statistical analyses
Incomplete outcome data addressed? All outcomes	Unclear risk	Based on evaluable subjects but small percentage lost to follow-up
Free of selective reporting?	Unclear risk	Same
Free of other bias?	Low risk	None detected
Hovestadt 1992		
Methods	Prospective, randomized, placebo controlled	
Participants	18 participants with epithelial ovarian cancer treated with cisplatin (75 mg/m ²) and cyclophosphamide (750 mg/m ²) every 3 weeks up to 9 cycles; 7 participants received Org 2766 and 11 participants served as controls	
Interventions	Org 2766 low dose (0.25mg/m ²) and high dose (1mg/m ²), immediately before cisplatin and 24 hours later	
Outcomes	Mean VPT in placebo treated participants were higher than in the low- and high-dose Org 2766 treated patients at 1 month, intermediate 1 to 4 months after treatment, and higher again after 4 to 12 and 12 to 24 months)	
Notes	Descriptive analysis only without formal statistical tests; the number of evaluable participants decreased during the study. The authors suggested that treatment with Org 2766 to prevent a cisplatin-induced neuropathy should possibly be continued up to four months after the last cycle of cisplatin	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Presumably but not described
Blinding? subject	Low risk	Placebo controlled
Blinding? observer	Low risk	Same
Blinding? All outcomes	Unclear risk	Presumably but not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Based on evaluable subject but substantial dropout
Free of selective reporting?	Unclear risk	Same
Free of other bias?	Low risk	None identified

Ishibashi 2010

Methods	Prospective, randomized, placebo controlled	
Participants	33 participants with metastatic colorectal cancer treated with FOLFOX, which included oxaliplatin, 85 mg/m ² every two weeks for six cycles; 17 Ca/Mg treated and 16 control participants	
Interventions	Ca (850 mg) and Mg (720 mg) infusions, before and after infusion of oxaliplatin or placebo	
Outcomes	The NCI Common Toxicity Criteria (NCI-CTC) and Debiopharm Neurotoxicity Scale (DEB-NTS)	
Notes	FOLFOX chemotherapy includes administration of 5-fluorouracil and l-leucovorin with each of six, two week treatment cycles	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized but method not specifically described
Allocation concealment?	Low risk	Centralized allocation via random number assignment
Blinding? subject	Low risk	Described as "double-blind" study
Blinding? observer	Low risk	Described as "double-blind" study
Blinding? All outcomes	Low risk	Yes, as above

Incomplete outcome data addressed? All outcomes	Low risk	Early termination of enrolment because of relatively "poorer" performance in the Ca/Mg group at interim analyses
Free of selective reporting?	Unclear risk	Yes, based on data to time of termination
Free of other bias?	Unclear risk	No evidence of other bias identified
Kanat 2003		
Methods	Prospective, randomized	
Participants	38 participants with non-small cell lung cancer treated with paclitaxel (175 mg/m ²) and carboplatin (AUC = 6) were randomized; 19 participants received amifostine and 19 participants served as controls	
Interventions	Amifostine 910 mg/m ² every 3 weeks × 6	
Outcomes	The mean SNAP amplitudes for both groups were comparable at baseline and also after six cycles of chemotherapy, there being no decline (clinically or statistically apparent) in the mean amplitudes for either group after treatment. paresthesias "grade 2" (reflecting an adverse sensory symptom outcome) developed in 8 of 19 participants in the carboplatin and paclitaxel plus amifostine group compared to 18 of 19 in the carboplatin and paclitaxel only group (P = 0.018)	
Notes	The authors concluded that the addition of amifostine to carboplatin and paclitaxel may prevent or reduce the incidence of neurotoxicity in the treatment of non-small cell lung cancer, but they cautioned in the text that the data from their trial were insufficient to support use of amifostine as a neuroprotective agent for paclitaxel and carboplatin chemotherapy	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized but method not described
Allocation concealment?	Unclear risk	Unclear, as not described
Blinding? subject	High risk	Randomized but no placebo
Blinding? observer	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	All data included
Free of selective reporting?	Unclear risk	No subjects dropped out of study
Free of other bias?	Low risk	None detected

Kemp 1996

Methods	Prospective, randomized	
Participants	242 participants with advanced ovarian cancer treated with cisplatin (100 mg/m ²) and cyclophosphamide (1000 mg/m ²) every 3 weeks × 6 cycles; 122 participants received amifostine 120 participants served as controls	
Interventions	Amifostine 910 mg/m ² pretreatment	
Outcomes	Neurotoxicity, defined as symptoms of peripheral neuropathy or a decrease in the neurological function daily activity score was related to the cumulative dose of cisplatin among participants with ovarian cancer who were treated with cisplatin and cyclophosphamide (Kemp et al., 1996). By treatment cycle 5, there was a significant difference (P = 0.015) between the groups, favoring the amifostine group. Following the last treatment cycle, the NCI neurologic toxicity rating (grades 0, 1, 2, or 3) was significantly reduced (P = 0.029) by pre-treatment with amifostine (122 participants pre-treated with amifostine, 120 control participants)	
Notes	The authors concluded that pre-treatment with amifostine reduced the neurotoxicity associated with cisplatin chemotherapy, based on reduction of the NCI toxicity rating scale	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized but method not described
Allocation concealment?	Unclear risk	Presumably, but not described

Blinding? subject	High risk	Randomized but not placebo controlled
Blinding? observer	Low risk	Evaluations performed by a third party blinded to treatment or adverse events
Blinding? All outcomes	Unclear risk	Same
Incomplete outcome data addressed? All outcomes	Unclear risk	Unclear if difference in dropouts between groups
Free of selective reporting?	Low risk	Used intent to treat analyses
Free of other bias?	Low risk	None identified

Lin 2006

Methods	Prospective, randomized, placebo controlled
Participants	14 participants with colorectal cancer treated with oxaliplatin (85 mg/m ² every two weeks for 12 cycles, plus weekly fluorouracil and leucovorin); 5 participants received NAC and 9 served as placebo controls
Interventions	NAC 1,200 mg one and one-half hours before each oxaliplatin treatment
Outcomes	Sensory (sural SNAP) amplitude, distal latency, and conduction velocity, and motor (median CMAP) amplitude, distal latency, conduction velocity, and F wave latency were measured at baseline and after 4, 8, and 12 cycles of chemotherapy. Clinical neurotoxicity was assessed every two weeks using the common toxicity criteria (CTC) of the NCI toxicity rating scale. After 12 cycles of treatment, the incidence of Grade 1, 2, and 3 neurotoxicity was 80, 20, and 0% among the 5 participants in the NAC group, respectively, and 100, 89, and 33% in the control group (P = 0.01)
Notes	The nerve conduction data were reported only for the NAC group, indicating no significant deterioration over the full trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? subject	Unclear risk	Described only as randomized and placebo controlled
Blinding? observer	Unclear risk	Presumably but not described
Blinding? All outcomes	Unclear risk	Presumably but not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described but all data evaluated
Free of selective reporting?	Unclear risk	Same
Free of other bias?	Unclear risk	No evidence of other bias identified

Lorusso 2003

Methods	Prospective, randomized
Participants	187 participants with ovarian cancer treated with carboplatin and paclitaxel every 21 days for 6 cycles.; 93 participants received amifostine and 94 participants served as controls
Interventions	Amifostine 910 mg/m ² pretreatment
Outcomes	Amifostine appeared to be protective against neurotoxicity (grade 3-4 neurotoxicity 3.7% versus 7.2%; P = 0.02)
Notes	The authors concluded that amifostine could exert some protection from the cumulative toxicity associated with carboplatin and paclitaxel

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated list
Allocation concealment?	Low risk	Randomization performed centrally to avoid bias
Blinding? subject	High risk	Not placebo controlled

Blinding? observer	Unclear risk	Performed by “dedicated” physicians but unclear if blinded
Blinding? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Based on evaluable subjects but small proportion of missing data
Free of selective reporting?	Unclear risk	Based on evaluable subjects
Free of other bias?	Low risk	None identified

Milla 2009		
Methods	Prospective, randomized, placebo controlled	
Participants	27 participants with colorectal cancer treated with FOLFOX4, which includes oxaliplatin (85 mg/m ² with each 2 week cycle up to 12 cycles) plus other agents (none known to be neurotoxic); 14 participants received GSH and 13 participants received saline placebo	
Interventions	GSH; 1500 mg/m ² before each oxaliplatin treatment	
Outcomes	At the end of treatment, only moderate neurotoxicity reported in the GSH arm (50% grade 1 and 50% grade 2), whereas in the placebo arm the neurotoxicity was more severe (69% grade 2 and 31% grade 3); the difference was considered statistically significant (Mann-Whitney test; P = 0.0037)	

Notes

Risk of bias		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? subject	Unclear risk	Described only as randomized and placebo controlled
Blinding? observer	Unclear risk	Presumably but not described
Blinding? All outcomes	Unclear risk	Presumably but not described
Incomplete outcome data addressed? All outcomes	Low risk	No dropouts (all data included)
Free of selective reporting?	Unclear risk	Not described but data from all subjects included
Free of other bias?	Unclear risk	No evidence of other bias identified

Pace 2003		
Methods	Prospective, randomized, placebo controlled (control patients were untreated)	
Participants	27 participants with various solid tumors (lung, ovarian, rhinopharyngeal, gastric, testicular, esophagus, ethmoid, and tongue cancer treated with cisplatin (cumulative dose > 300 mg/m ²); 13 participants treated with vitamin E and 14 participants served as controls	
Interventions	Vitamin E 300 mg/day starting before cisplatin and continuing up to 3 months after cisplatin treatment	
Outcomes	The median SNAP amplitudes were reduced by a greater degree in those without vitamin E than those taking vitamin E (Without group: Baseline 14.5 ± 8.5 μV; 6 months later 13.6 ± 9.2 μV; Vitamin E group: baseline 15.5 ± 6.3 μV; 6 months later 13.7 ± 5.5 μV) The differences between sural SNAPs in the two groups were not significant	
Notes	Of 47 patients enrolled, 20 dropped out mainly for disease progression. Clinical impairment on neurological examination was measured by an unvalidated scale. The authors concluded that supplemental vitamin E decreases incidence and severity of neurotoxicity	

Risk of bias		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized but method not described
Allocation concealment?	Unclear risk	Not described
Blinding? subject	High risk	Subjects were not blinded

Blinding? observer	High risk	Neurologists performing examinations were not blinded to treatment status
Blinding? All outcomes	Unclear risk	Not described, although neither the subjects nor neurologists were blinded
Incomplete outcome data addressed? All outcomes	Unclear risk	Based on evaluable subjects, although substantial drop out
Free of selective reporting?	Unclear risk	Same
Free of other bias?	Low risk	None identified

Planting 1999

Methods	Prospective, randomized, placebo controlled	
Participants	74 participants with advanced head and neck cancer treated with cisplatin (70 mg/m ² weekly); 37 participants received amifostine and 37 participants served as controls	
Interventions	Amifostine 740 mg/m ² immediately before cisplatin	
Outcomes	Participants receiving amifostine showed significantly less subclinical neurotoxicity as measured by the VPT relative to controls	
Notes	The authors explained that the borderline significant group difference for the right hand VPT reflected an imbalance at baseline for the groups and limited data. The authors concluded that amifostine reduced the risk of subclinical neurotoxicity caused by cisplatin but did not result in a higher cisplatin dose intensity	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized but method not described
Allocation concealment?	Unclear risk	Not described
Blinding? subject	Unclear risk	Not described
Blinding? observer	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Low risk	Based on evaluable data but limited drop out
Free of selective reporting?	Unclear risk	Same
Free of other bias?	Low risk	None identified

Roberts 1997

Methods	Prospective, randomized, placebo controlled	
Participants	196 participants with epithelial ovarian cancer treated with cisplatin (75 to 100 mg/m ²) and cyclophosphamide (600 to 1000 mg/m ²); 129 participants treated with Org 2766 and 67 participants served as controls	
Interventions	Org 2766 2 mg/m ² or 4 mg/m ²	
Outcomes	VPT increased during the study, independent of receiving Org 2766, with no difference in the rate of change or the degree of neuropathy	
Notes	No evidence of efficacy in preventing or slowing development of neuropathy. The authors concluded that no benefit could be demonstrated using Org 2766 and suggested that high Org 2766 dose might eventually increase the peripheral neurotoxicity of cisplatin	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized but method not described
Allocation concealment?	Unclear risk	Same
Blinding? subject	Low risk	Described as blinded, placebo controlled study
Blinding? observer	Unclear risk	Presumably, but not described

Blinding? All outcomes	Unclear risk	Same
Incomplete outcome data addressed? All outcomes	Low risk	Based on evaluable subjects but limited drop out
Free of selective reporting?	Low risk	Same
Free of other bias?	Low risk	None identified

Schmidinger 2000

Methods	Prospective, randomized, placebo controlled
Participants	20 participants with non-small cell lung cancer (NSCLC) and head and neck cancer treated with cisplatin (80 mg/m ² × every 4 weeks); 11 participants treated with GSH and 9 participants served as controls
Interventions	GSH 5g/m ² before cisplatin or placebo
Outcomes	No difference in clinical or nerve conduction measurement between the two groups
Notes	The authors concluded that the combination of GSH and cisplatin was safe and the antitumor efficacy of cisplatin not impaired, identified no difference between GSH-treated and control groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized but method not described
Allocation concealment?	Unclear risk	Same
Blinding? subject	Unclear risk	Not specifically described
Blinding? observer	Unclear risk	Same
Blinding? All outcomes	Unclear risk	Same
Incomplete outcome data addressed? All outcomes	Low risk	Based on evaluable subjects but only 1 subject dropped out (in control group)
Free of selective reporting?	Low risk	Same
Free of other bias?	Low risk	None identified

Smyth 1997

Methods	Prospective, randomized, placebo controlled
Participants	151 participants with ovarian cancer treated with cisplatin (100 mg/m ² × every 3 weeks × 6 courses); 74 participants received GSH and 77 participants served as controls
Interventions	GSH 3 G/m ² before cisplatin
Outcomes	Mean increase in HAD 0.8 in GSH and 2.5 in P (depression score) 45 of 47 in Rotterdam had better scores in GSH
Notes	Participants reported improvement in QOL if received GSH Significantly less tingling in hands and feet. GSH allowed more cycles of cisplatin because of less toxicity. The authors concluded that participants receiving GSH had a clear improvement in quality of life with significantly less tingling in their hand and feet and received more cycles of cisplatin because of less toxicity

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated
Allocation concealment?	Low risk	Central randomization
Blinding? subject	Unclear risk	Presumably (placebo controlled) but not described
Blinding? observer	Unclear risk	Same
Blinding? All outcomes	Unclear risk	Same
Incomplete outcome data addressed? All outcomes	Unclear risk	Based on evaluable subjects but substantial drop out

Free of selective reporting?	Unclear risk	As above, analyses performed on relatively small subset of evaluable subjects
Free of other bias?	Low risk	None identified
van Gerven 1994		
Methods	Prospective, randomized, placebo controlled	
Participants	42 participants with testicular and adenocarcinoma of unknown primary treated with cisplatin (100 mg/m ² for at least 4 cycles) and with different combinations of etoposide, bleomycin and ifosphamide; 19 participants treated with Org 2766 and 23 participants served as controls	
Interventions	Org 2766 2 mg/d × 5 days or placebo	
Outcomes	Borderline-significant difference in degree of VPT favoring Org2766 versus placebo. Symptom scores not significantly different	
Notes	The authors indicated that Org 2766 cannot completely prevent cisplatin neuropathy but may ameliorate nerve damage	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized but method not described
Allocation concealment?	Unclear risk	Same
Blinding? subject	Unclear risk	Not described
Blinding? observer	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Based on subjects completing 4 cycles of chemotherapy
Free of selective reporting?	Low risk	As above, few eligible subjects had missing data
Free of other bias?	Low risk	None identified

van-der-Hoop 1990

Methods	Prospective, randomized, placebo controlled	
Participants	55 participants with epithelial ovarian cancer treated with cisplatin (75 mg/m ²) and cyclophosphamide (750 mg/m ²); 33 participants received Org 2766 and 22 participants served as controls	
Interventions	Org 2766 low dose (0.25 mg/m ²) and high dose (1 mg/m ²), immediately before and after cisplatin	
Outcomes	In the high dose Org 2766 group, the VPT increased about 2-fold, significantly less than the nearly 8-fold increase in the placebo group	
Notes	The authors felt that Org 2766 prevented or attenuated cisplatin neuropathy	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized but method not described
Allocation concealment?	Low risk	Done before study and treatment codes not revealed to clinicians
Blinding? subject	Low risk	Yes, placebo controlled
Blinding? observer	Low risk	Treatment codes not revealed to clinicians
Blinding? All outcomes	Low risk	Same
Incomplete outcome data addressed? All outcomes	Low risk	Yes, intention to treat analyses based on all enrolled subjects
Free of selective reporting?	Low risk	Same
Free of other bias?	Low risk	None identified

VPT: vibration perception threshold

GSH: Glutathione

NIS: Neuropathy Impairment Scale

NSS: Neuropathy Symptom Scale

PN: peripheral neuropathy

SNAP: Sensory nerve action potential

SCLC: small cell lung cancer

NSCLC: non small cell lung cancer

DDTC: diethyldithiocarbamate

AUC: area under the curve

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Argyriou 2005	Unable to separate the effects of cisplatin from those of paclitaxel (Taxol)
Block 2005	Review article
Bogliun 1992	Neither the control group nor the intervention group developed neurotoxicity, so unable to assess efficacy
Capizzi 1995	Review article
Cassidy 1998	Randomized, placebo controlled trial that was discontinued prematurely because of nausea and vomiting, limiting analyses. Nevertheless, the available data suggested that nimodipine exacerbated (not prevented) neurotoxicity
Catalano 1999	Abstract
Culy 2001	Review article
De Grandis 2007	Review article
DeVos 2005	Unable to separate the effects of carboplatin from those of paclitaxel
Durand 2003	Reports of treatment of acute sensory symptoms, not prevention of neuropathy
Gamelin 2004	Retrospective, non-randomized study.
Gamelin 2008	Letter
Gedlicka 2003	Letter
Gispen 1992	No details of study provided
Glover 1987	Phase I trial
Glover 2003	Treatment schedule not comparable
Grothey 2005	Review article
Haigentz 2003	Phase I trial
Heidenreich 1999	Limited information
Hensley 2009	Description of practice guideline
Hilkens 1995	Study involved dosing of cisplatin
Hilpert 2005	Unable to separate the effects of carboplatin from those of paclitaxel
Hochster 2007	Letter
Kesari 2005	Letter
Leong 2003	Only two doses of carboplatin
Lissoni 1997	Details of neuropathy not provided
Lissoni 1999	Groups not comparable and previous therapy unknown
Lissoni 2002	Not a randomized trial
Miller 2008	Unable to separate the effects of cisplatin from those of docetaxel
Mollman 1988	Study of risk factors associated with cisplatin neuropathy
Pace 2005	Letter
Pace 2010	Substantial dropout rate, excluding intention-to-treat analyses
Penz 2001	Pilot study, not controlled trial
Rick 2001	Open label, unblinded trial
Wang 2007	Randomized but neither blinded nor placebo controlled
Wilkes 2007	Review article