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Systematischer Review zur medikamentösen Prävention und Therapie Chemotherapie-induzierter peripherer Polyneuropathie

Dissertation
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Systematic Review for the Medicinal Prevention and Treatment of Chemotherapy-Induced Peripheral Polyneuropathy

Thesis
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Human Medicine

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Referat

Die periphere Polyneuropathie ist eine sehr häufige und für die PatientInnen belastende Nebenwirkung der Chemotherapie (CTX) bei Krebspatienten. Neben der negativen Beeinflussung der Lebensqualität kommt es vermehrt zu Therapieabbrüchen sowie Dosisreduzierungen der anti-neoplastischen Therapie und damit zu höheren Rezidivraten, erhöhter Morbidität und Mortalität.

Diese Dissertationsarbeit entstand im Rahmen der S3- Leitlinie für "Supportive Therapie bei onkologischen PatientInnen". Zielsetzung war es, einen Überblick über die sich qualitativ unterscheidenden Studien und deren häufig kontroversen Ergebnisse zu geben sowie eine Aussage über die Anwendung möglicher Substanzen zur Prävention und Therapie der Chemotherapie- induzierten peripheren Polyneuropathie (CIPN) zu treffen.

Die Ergebnisse und die Qualität randomisiert- kontrollierter Studien (RCTs) zur Wirksamkeit supportiver Therapien in der Prävention und Therapie der CIPN wurden hierzu bewertet und deren Behandlungseffekte, wenn möglich, in Metaanalysen zusammengefasst. Drei Datenbanken wurden systematisch nach RCTs in deutscher und englischer Sprache durchsucht. Weiterhin erfolgte eine ausführliche Handsuche. Es konnten 58 RCTs und drei systematische Übersichtsarbeiten identifiziert werden.

Für keine der Substanzen, die in den Studien oder Metaanalysen untersucht wurden, konnte eine uneingeschränkte Empfehlung zur medikamentösen Prävention der CIPN gegeben werden. Die Ergebnisse waren häufig widersprüchlich oder die Substanz verursachte nicht zu tolerierende Nebenwirkungen. Zur Therapie der CIPN sollte die Gabe von Duloxetin und bei limitierten Therapieoptionen von Amitryptilin, Gabapentin und Venlafaxin erwogen werden.

Aufgrund der heterogenen Behandlungseffekte und der qualitativ stark differenten Studien sowie der uneinheitlichen Methodik zur Erhebung der CIPN besteht weiterhin Forschungsbedarf, um einerseits geeignete, leicht durchführbare und valide Erhebungsmethoden der CIPN zu identifizieren und andererseits wirksame, nebenwirkungsarme und im klinischen Alltag anwendbare Substanzen zur Prävention und Therapie der CIPN zu finden.

Diese Dissertationsschrift wurde in englischer Sprache geschrieben, da fast ausschließlich englisch sprachige Originalliteratur erfasst wurde und die Arbeit ein Teil der S3- Leitlinie ist.

Beckmann, Juliane: Systematischer Review zur medikamentösen Prävention und Therapie Chemotherapie-induzierter peripherer Polyneuropathie; Halle (Saale), Univ., Med.Fak., Diss., 165 Seiten, 2016

Abstract

Chemotherapy- induced peripheral neuropathy (CIPN) is a very common and burdening side effect of antineoplastic therapy in cancer patients.

It leads to detoriation of quality of life, dosage reductions of the chemotherapy, a higher number of discontinuation of the therapy and thus, to higher recurrence rates, morbidity and mortality.

This dissertation is part of the S3- guideline "Supportive therapy in cancer patients".

Purpose of this work was to investigate the difference of quality and the often controversial results of the studies included. Finally, a statement about the usage of possible agents to prevent or treat CIPN should be delivered.

Therefore, treatment effects and quality of randomized controlled trials (RCTs) were graded and as far as possible pooled in meta- analyses.

Three electronic data bases were searched systematically for RCTs on prevention and treatment of CIPN in German or English language. In addition a detailed hand search was performed. Fifty-eight RCTs and three systematic reviews (SR) were identified.

For none of the substances an unlimited recommendation regarding the prevention of CIPN could be given. Results often were controversial or the agent investigated showed other side effects which were not tolerable.

For the therapy of CIPN the usage of duloxetine is recommended and considering the limited therapeutic options, amitryptiline, gabapentin and venlafaxine can be used.

Since the quality of studies and treatment effects was very heterogeneous and methods of detecting CIPN varied largely, further high quality studies should be performed. On one hand, they should be aimed to find easy to perform and valid methods to detect CIPN and on the other hand to identify secure and effective agents to prevent and treat CIPN.

This dissertation is written in English language since references were mainly published in English and this thesis is part of the S3- guideline.

Beckmann, Juliane: Systematischer Review zur medikamentösen Prävention und Therapie Chemotherapie-induzierter peripherer Polyneuropathie; Halle (Saale), Univ., Med.Fak., Diss., 165 Seiten, 2016

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List of abbreviations

5-ASA	5-Aminosalicylacid
5-FU	5-Fluorouracil
ACC	Acetylcysteine
ADL	Activities of Daily Life
ALA	Alpha- lipoic acid
ALC	Acetyl-L-Carnitine
AUC	Area Under the Curve
BPI	Brief Pain Inventory
CA	Carcinoma
CEBM	Centre for Evidence-Based Medicine
CENTRAL	Cochrane Centre Register of Controlled Trials
CI	Confidence Intervall
CIPN	Chemotherapy-Induced Peripheral Neuropathy
CMAP	Compound Muscle Action Potential
CR	Complete Response
CTX	Chemotherapy
d	Day(s)
DDTC	Diethyldithiocarbamate
ECOG	Eastern Cooperative Oncology Group
ENS	ECOG Neuropathy Scale
EMG	Electromyography

EORTC-QlQ-CIPN 20	European Organization for Research and Treatment of Cancer Chemotherapy-induced peripheral neuropathy (CIPN) 20-item quality of life questionnaire
f	Female
FACT	Functional Assessment of Chronic Illness Therapy
FACT-GOG/Ntx	FACT- Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients
FOLFOX	Folinic Acid (Leucovorin), Oxaliplatin und Bolus Fluorouracil
GRADE	Grading of Recommendations, Assessment, Development and Evaluation Working Group
GSH	Glutathione
HADS	Hospital Anxiety and Depression Score
i.m.	Intramuscular
ITT	Intention To Treat
IU	International Units
i.v.	Intravenous
KIM IV	Klinik für Innere Medizin IV- Clinic for Internal Medicine
m	Male
MD	Mean Difference
Medline	MEDLARS online (“Medical Literature Analysis and Retrieval System”)
n	Number
NCI-CTCAE	National Cancer Institute- Common Terminology Criteria for Adverse Events
NCV	Nerve Conduction Velocity

NDS	Neurologic Disability Score
NPS	Neuropathic Pain Scale
NRS	Numeric Rating Scale
NSPI	Neuropathic Pain Symptom Inventory
NSS	Neurologic Symptom Score
OFA	Omega-3 fatty Acids
OR	Odds Ratio
OS	Overall Survival
OSS	Oxaliplatin Specific Scale
OXC	Oxcarbazepine
Pat.	Patients
PFS	Progression-Free Survival
p.o.	Per os
POMS	Profile Of Mood State
PR	Partial Response
PRISMA	Preferred Reporting Items of Systematic Reviews and Meta Analyses
QoL	Quality of Life
QST	Quantitative Sensory Testing
RCT	Randomized Controlled Trial
rhuLIF	Recombinant human Leukemia Inhibitory Factor
RR	Risk Ratio
rTNS	Reduced Total Neuropathy Score
s.c.	Subcutaneous

SIGN	Scottish Intercollegiate Guidelines Network
SNAP	Sensory Nerve Action Potential Amplitudes
SR	Systematic Review
TC	Taxane and Carboplatin
TEC	Taxane Epirubicin Carboplatin
TNS	Total Neuropathy Score
TR	Tumor Response
TTF	Time to Treatment Failure
TTP	Time to Progression
VAS	Visual Analogue Scale
VDS	Verbal Descriptive Scale
VPT	Vibration Perception Threshold
WHO	World Health Organization

1 Introduction

1.1 Background and objectives

Antineoplastic agents often appear to be neurotoxic. Chemotherapy-induced peripheral neurotoxicity (CIPN) is a common side effect and a reason for discontinuation or dose reduction of chemotherapy and also responsible for higher mortality and morbidity in cancer patients. The sensory chronic peripheral form is the most common kind of neuropathy induced by chemotherapy (Galer 1998, Cavaletti and Marmiroli 2010, Albers *et al.* 2011).

Due to CIPN, patients often want to intermit or reduce chemotherapy which decreases the chance of complete tumor response or shortens time to progression.

Additionally, CIPN affects quality of life and compromises activities of daily life (ADL).

Patients struggle with common procedures in daily living such as unbuttoning or handiworks. Besides the personal disappointment and anger being unable performing thus far common activities, sensor or motor CIPN and additionally, neuropathic pain, can thwart the chance to go back into employment or social activities.

Furthermore, CIPN causes more frequent and longer hospital stays and health care costs. A flow chart of the consequences of CIPN can be seen in figure 1 (Tofthagen *et al.* 2013, Loprinzi *et al.* 2014).

The incidence of CIPN varies largely from approximately 10% up to 100%, according to the antineoplastic agent and regimen, the number of cycles administered, the cumulative dose, the method assessing CIPN and patient characteristics (Visovsky and Daly 2004, Cavaletti and Marmiroli 2010, Hershman *et al.* 2014). The overall incidence of CIPN is estimated to be 38% (Hershman *et al.* 2014).

This SR shall be focused on antineoplastic agents with especially high incidences of CIPN such as platinum drugs, vinca alkaloids, taxanes and bortezomib. For simplicity, the term "CIPN" will be used in this dissertation work although knowing that for example bortezomib is no classic chemotherapeutic agent.

In clinical studies only ≥grade 2 neuropathy is often reported. However it should not be underestimated that also grade 1 and 2 CIPN can extremely compromise the patient's quality of life and ADLs.

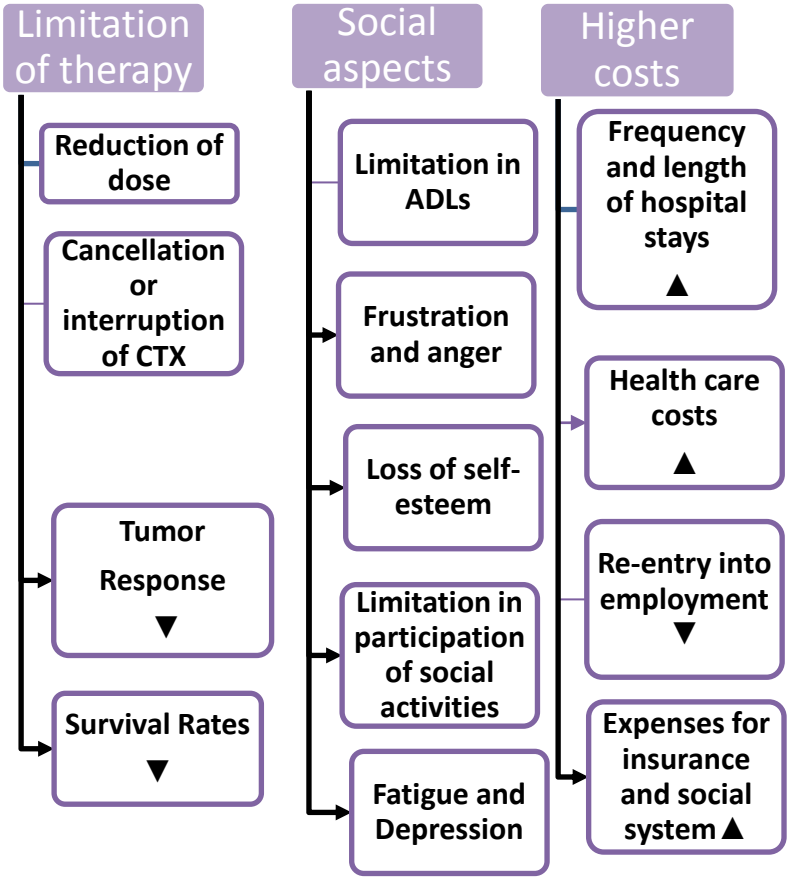

Figure 1: Consequences of chronic chemotherapy- induced peripheral neuropathy ▲: increase ▼: decrease (modified according to: (Cleeland *et al.* 2010, Albers *et al.* 2011, Alberti *et al.* 2014)

A common method to assess neurotoxicity as one side effect of chemotherapy is the National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI-CTCAE) (see Table 1) (National Cancer Institute 2009).

Rating CIPN as a common and compromising side effect of chemotherapy, it was adopted as a part of the German S3- guideline for "Supportive Care in Cancer Patients" (Alt-Epping *et al.* 2015). The guideline was coordinated by Prof. Dr.med. Karin Jordan and Dr. med. Franziska Jahn from January 2013 until September 2016. It is aimed to support doctor's daily decisions in clinical practice based on scientific evidence.

S3- guidelines dispose of high methodical quality since all data were searched systematically, extracted information were consented by a committee of experts and their quality was graded.

1.2 Pathogenesis and definition of chemotherapy- induced peripheral neuropathy

Pathogenesis of CIPN consists of different complex mechanisms which are still matter of recent research. In this thesis, only an insight of the pathogenesis of CIPN shall be given.

In general, symptoms are expression of axonal damage and damage of cells of the nervous system. These cells seem to be very sensitive to the toxic effects of antineoplastic agents (Brzeziński 2012). In pathogenesis and clinical symptoms acute CIPN needs to be differentiated from the chronic manifestation. Additionally, different chemotherapeutics lead to distinct effects on the nervous system. Whilst chronic CIPN triggered by platinum compounds is caused by apoptosis of the dorsal root ganglia, the acute form, mainly appearing when oxaliplatin is administered, is determined by oxalate-induced failure of voltaged natrium channels of the axon. Taxanes lead to excessive tubulin- polymerisation. An acute syndrome of arthralgias and muscle pain can appear when high dosages of paclitaxel are administered (Loprinzi *et al.* 2011). Meanwhile, vinca alkaloids destroy microtubules and thus effect axonal transport**.** Results on research with bortezomib suggest effects on the dorsal root ganglion and on the peripheral axons caused by interference with nuclear processes (Grisold *et al.* 2012).

Considering the clinical symptoms of the chronic and the acute manifestation of CIPN, the chronic form mainly consists of sensory symptoms such as numbness, paresthesia, cold hyperalgesia, distribution of proprioception and neuropathic pain which appear distal and symmetric. Patients commonly report “glove and stocking-like” distribution.

Sensory symptoms get worse along the course of treatment, as they are usually dose dependent, explained in part by the progress of morphological nerve damage. CIPN is known to be partially reversible in 80% of the patients. Forty percent experience total regression. The “coasting effect” describes the phenomenon that CIPN is still progressing for two to six month even though chemotherapy has been already finished. Although motor symptoms and autonomic function impairment are more unlikely to appear, they still can be a part of chronic CIPN (Galer 1995, Backonja *et al.* 1998, Hershman *et al.* 2014).

Acute CIPN, especially caused by taxols and oxaliplatin appears as a neuropathic pain syndrome, one to three days after administration of chemotherapy. Symptoms caused by oxaliplatin are cold-triggered paresthesias, swallowing discomfort or jaw and muscle cramps. They are commonly reversible within one week. This acute pain syndrome cannot be explained by axonal damage. It is more likely that oxaliplatin has a direct nerve-exiting effect as described above (Gamelin *et al.* 2004, Lipp 2005, Grothey *et al.* 2011).

1.3 Assessment of chemotherapy-induced neuropathy

CIPN has no standard tool for assessment. Many different methods lead to a lack of comparability and make it difficult to pool data. As a subjective complex of symptoms it is remarkably hard to generate an objective, exact and valid method for assessment. The assessment method should be able to differentiate chemotherapy- induced neuropathic symptoms from other pre-existing components of neuropathies of other pathogenesis. As well, it should describe the spectrum of neuropathic symptoms and impairments and report about their grade and development along the course of chemotherapy and treatment. Additionally, the assessment must be easy to use in clinical practice (Cleeland *et al.* 2010).

Subjective assessments taken from doctor's or patient's perspective need to be differentiated from quantitative methods. In clinical practice, CIPN is mainly diagnosed and observed through anamnesis and clinical examination of deep tendon reflexes, motor and sensor functions. Thus, this method is dependent on the patient's compliance and it is not independent from the doctor's appraisal.

Many studies use severity rating scales. Patient reported outcomes and clinical symptoms are often displayed in CTC (see table 1) and WHO criteria. They are commonly used since they are easy to perform, to compare and to repeat (Cavaletti *et al.* 2006, Cleeland *et al.* 2010, Cavaletti *et al.* 2013, Alberti *et al.* 2014).

Table 1: CIPN NCI-CTCAE sensor and motor neuropathy. Version 4.03
(National Cancer Institute 2009)

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care	ADL Life-threatening consequences; urgent intervention indicated	Death
Definition: **A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.**					
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: **A disorder characterized by inflammation or degeneration of the peripheral motor nerves.**					

Semi-quantitative testing such as sensory perception threshold are not standardized and thus questionable for grading CIPN. Quantitative tests such as sensory nerve action potentials amplitudes (SNAP) are another way to examine CIPN. They can show subclinical changes and are important for distinguishing CIPN from other neuropathies. Nevertheless, they often do not correlate with clinical changes and severity. In addition, various methods, testing of numerous nerves and various equipment make it hard to assess comparable and repeatable data.

The results of different assessment methods are often summed and displayed in neurotoxicity scales such as the Total Neuropathy Score (TNS) (see table 2).

Furthermore patient's subjective parameters can be surveyed in quality of life questionnaires. Commonly used questionnaires are the Functional Assessment of Cancer Therapy (FACT-G) score or the European Organization for Research and Treatment of Cancer-Chemotherapy-induced peripheral neuropathy- 20-item quality of life questionnaire (EORTC-CIPN 20) (Postma and Heimans 2000).

Table 2: Total Neuropathy Score (TNS): 0 no neuropathy, 1-9 mild, 10-19 moderate and ≥20 severe neuropathy
(Postma and Heimans 2000, Cavaletti *et al.* 2006, Smith *et al.* 2008)

Parameter	0	1	2	3	4
Sensory symptoms	None	Symptoms limited to finger or/and toes	Symptoms extend to ankle	Symptoms extend to knee or/and elbow	Symptoms above knee/elbow, functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help or assistance	Paralysis
Number of autonomic symptoms	None	One	Two	Three	Four or five
Pin sensibility	Normal	Reduced in finger or/and toes	Reduced up to twist or/and ankle	Reduced up to elbow or/and knee	Reduced above to elbow or/and knee
Vibration sensibility	Normal	Reduced in finger or/and toes	Reduced up to twist or/and ankle	Reduced up to elbow or/and knee	Reduced above to elbow or/and knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflexes	Normal	Ankle reflexes reduced	Ankle reflexes absent	Ankle reflexes absent, others reduced	All reflexes absent

Any of the named methods have advantages and disadvantages and are suitable for different issues and interests.
Worldwide, the NCI-CTCAE criteria are most commonly used.

It is recommended to perform a neurologic anamnesis and status combined with patient reported outcomes, e.g. questionnaires, before applying any neurotoxic agent and repeat examination or questionnaires after every cycle and after follow-up (Alberti *et al.* 2014)

2 Methods

This SR originated in the development of a clinical practice S3- guideline for "Supportive care in cancer patients". The guideline was established from January 2013 until September 2016 at the University Hospital of Halle, Clinic of Internal Medicine (KIM IV). The guideline was coordinated by apl. Prof. Dr. med. Karin Jordan and Dr. med. Franziska Jahn. When the guideline was acquired all important associations and working committees were present (see table 3).The project was established within the German framework of the guideline program of Oncology and supported by the German Cancer Aid. This guideline was initiated under the mandate of the "Arbeitsgemeinschaft für Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin- ASORS" (Working Group for Oncology, Rehabilitation and Social Medicine), the "Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie- DGHO" (German Association for Haematolgy and Medical Oncology) and the "Deutschen Gesellschaft für Radioonkologie e.V.- DEGRO" (German Association for Radiooncology).

The used methods are based on the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Higgins and Green 2011) and correspond to *AMSTAR criteria on performance and PRISMA criteria on reporting (Shea et al. 2007, Moher et al. 2009)*.

Table 3: Participating associations, working groups and organizations

Associations, Working groups and organizations	
Deutsche Dermatologische Gesellschaft (DDG)	German Association for Dermatology
Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV)	German Association for General and Visceral Surgery
Deutsche Gesellschaft für Chirurgie e.V. (DGCH)	German Association for Surgery
Deutsche Gesellschaft für Innere Medizin e.V. (DGIM)	German Association for Internal Medicine
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)	German Association for Haematology and Medical Oncology
Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM)	German Association for General Practice and Family Medicine
Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (DGVS)	German Association for Digestion and Metabolic Diseases
Deutsche Gesellschaft für Mund-, Kiefer- und	German Association for Oral and Dentofacial

Table 3: Participating associations, working groups and organizations

Associations, Working groups and organizations	
Gesichtschirurgie (DGMKG)	Surgery
Deutsche Krebsgesellschaft (DKG)	German Association for Cancer
Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)	German Association for Gynecology and Obstetrics
Deutsche Gesellschaft für Neurologie (DGN)	German Association for Neurology
Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Halschirurgie e.V.	German Association for Otolaryngology, Head and Neck Surgery
Deutsche Gesellschaft für Osteologie e.V. (DGO)	German Association for Osteology
Deutsche Osteoonkologische Gesellschaft (DOG)	German Association for Osteooncology
Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)	Association for Pediatric Oncology and Haematology
Deutsche Gesellschaft für Orthopädie und Orthopädische Chirurgie e.V. (DGOOC)	German Association for Orthopedics and Orthopedic Surgery
Deutsche Gesellschaft für Palliativmedizin (DGP)	German Association for Palliative Care
Deutsche Gesellschaft für Radioonkologie (DEGRO)	German Association for Radiooncology
Deutsche Gesellschaft für Urologie e.V. (DGU)	German Association for Urology
Deutsche Gesellschaft für Senologie e.V.	German Association for Senology
Deutsche Gesellschaft für Neurochirurgie e.V. (DGNC)	German Association for Neurosurgery
Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP)	German Association for Pneumology and Ventilation Therapy
Deutsche Gesellschaft für Thoraxchirurgie (DGT)	German Association for Thoracic Surgery
Deutsche Gesellschaft für Onkologische Pharmazie (DGOP)	German Association for Oncologic Pharmacy
Österreichische Gesellschaft für Hämatologie und Onkologie (OeGHO)	Austrian Association for Haematology and Oncology
Schweizerische Gesellschaft für Onkologie	Swiss Association for Oncology

Table 3: Participating associations, working groups and organizations	
Associations, Working groups and organizations	
(SGMO)	
Haus der Krebsselbsthilfe	House of cancer self help
Bundesverband niedergelassener Hämatologen und Onkologen (BNHO)	Federal Association of Resident Haematologists and Oncologists
Berufsverband Deutscher Strahlentherapeuten (BVDST)	Professional Association of Radiotherapists
Arbeitsgemeinschaft Prävention und integrative Medizin in der Onkologie (PRIO)	Working Group Prevention and Integrative Medicine in Oncology
AG Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin (ASORS)	Working Group for Supportive Care in Oncology, Rehabilitation and Social Medicine
Konferenz onkologischer Kranken- und Kinderkrankenpflege (KOK)	Conference of Oncologic Nursing and Pediatric Nursing
Zentralverband der Physiotherapeuten / Krankengymnasten	Central Organization of Physiotherapists and Medical Gymnastics
Arbeitsgemeinschaft Radiologische Onkologie (ARO)	Working Group for Radiologic Oncology
Arbeitsgemeinschaft Internistische Onkologie (AIO)	Working Group for Internistic Oncology
Arbeitsgemeinschaft Palliativmedizin (APM)	Working Group for Palliative Care
AG Hals-Nasen-Ohren-Heilkunde, Mund-Kiefer-Gesichtschirurgische Onkologie (AHMO)	Working Group for Oncologic Otolaryngology and Orofacial Surgery
Arbeitsgemeinschaft für Psychoonkologie (PSO)	Working Group for Psychooncology
Chirurgische Arbeitsgemeinschaft Onkologie (CAO)	Surgical Working Group for Oncology
Chirurgische Arbeitsgemeinschaft Onkologie-Viszeralchirurgie (CAO-V)	Surgical Working Group for Oncology-Visceral Surgery
Neuroonkologische Arbeitsgemeinschaft (NOA)	Neurooncologic Working Group
Arbeitsgemeinschaft für onkologische Pharmazie (OPH)	Working Group for Oncologic Pharmacy

Table 3: Participating associations, working groups and organizations	
Associations, Working groups and organizations	
Arbeitsgemeinschaft Dermatologische Onkologie (ADO)	Working Group for Dermatologic Oncology
Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)	Working Group for Gynecologic Oncology
Arbeitsgemeinschaft Urologische Onkologie (AUO)	Working Group for Urologic Oncology
Pneumologisch-Onkologische Arbeitsgemeinschaft (POA)	Pneumologic Oncologic Working Group
Deutsches Netzwerk Evidenzbasierte Medizin e.V. (DNebM)	German Network for Evidence Based Medicine

2.1 Objectives

The objective of this dissertation thesis is to perform a SR including meta-analyses on the basis of RCTs and pre-existing SRs dealing with prevention and treatment of CIPN, regarding all English and German literature. This work shall be focused on platinum derivates, taxanes, vinca alkaloids and bortezomib, since these substances extremely often lead to CIPN. Comparing and grading the evidence of the trials is crucial for being able to give recommendations. These recommendations are part of the S3- guideline "Supportive Therapy in cancer patients". In the kick-off meeting in 2013, therefore the following key questions regarding CIPN were consented by 50 experts and elected representatives. The fourth and fifth questions were searched de novo and are objective of this dissertation.

1. How often does the described antitumor therapy lead to peripheral neuropathy?

2. Which individual and substance specific risk factors exist which increase the probability to suffer from chemotherapy- induced peripheral neuropathy?

3. Which diagnostic methods ensure an early and secure diagnosis of chemotherapy-induced peripheral neuropathy?

4. **Regarding "complete response" when application of one of the named substances[1] is planned, which strategy of the prevention or prophylaxis of peripheral neuropathy is best?**

5. **Which therapeutic strategy is superior when signs and symptoms of chemotherapy-induced peripheral neuropathy have already occurred?**

[1] Bortezomib, Oxaliplatin, Cisplatin, Carboplatin, Paclitaxel, Docetaxel, Cabazitaxel, Vincalkaloid, Lenalidomid, Thalidomid, Tyrosinkinaseinhibitoren, Epothilone

2.2 Criteria for inclusion of studies

The criteria for the inclusion of studies are based on the PICO scheme. It helps to define a focused clinical question and makes it easier to search for precise answers and literature.

The PICO format includes the following items (Schardt *et al.* 2007):

- Which **p**atient, population or problem is addressed?
- Which **i**ntervention shall be investigated?
- Which **c**omparison or exposure is in focus?
- Which **o**utcome is researched?

According to the PICO frame work we searched for studies fulfilling the following terms:

Types of studies

We considered all RCTs and SRs including RCTs in which the efficacy of any neuroprotective agent against chemotherapy- induced peripheral neurotoxicity was investigated. Blinded and un-blinded RCTs were considered. Studies had to be designed to investigate prevention or treatment of CIPN. Supportive experimental therapy was compared to placebo, no treatment or other treatments.

We only searched for human trials in English or German language. Only full text articles and reviews were included. Published abstracts were excluded since they only contain selective information and the bias of missing data is too high.

Participants

Only adult persons (≥18 years) of either sex undergoing chemotherapy with any agent against cancer were included. The kind of cancer, state of cancer or weather a combination of chemotherapy and radiotherapy was applied did not matter for inclusion.

Interventions

Interventions were all medicinal supportive schemes for prevention or therapy of CIPN.

Outcome measures

Primary Outcome Measures

After discussion, simply the occurrence of chemotherapy-induced peripheral neurotoxicity has been selected as the primary outcome of this review, no matter which assessment method has been used, for the following reasons:

1) This review is dealing with studies investigating the effect of anti-neurotoxic substances. The agents investigated shall not interfere with anti-tumor efficacy. Possible differences between the study groups concerning survival or tumor response were considered as secondary outcomes.

2) Many studies did not report survival data such as overall survival (OS) or progression- free survival (PFS).

3) As described above, there is no standard assessment for CIPN.

Earlier studies mainly used electro-physiologic measurements (e.g.: vibration perception threshold (VPT), nerve conduction velocity (NCV)) while later trials investigated neurotoxicity rather through patient questionnaires and patient assessments (Hovestadt *et al.* 1992, Cleeland *et al.* 2010, Alberti *et al.* 2014).

The National Cancer Institute Common Terminology Criteria for adverse events (NCI-CTCAE, versions 2.0- 4.0) for peripheral neuropathy have been used in many trials. NCI-CTC scales have the advantage to be easy to use and can be applied for many different kinds of antineoplastic agents (Cleeland *et al.* 2010).

Although, this method has also its limitations we preferred this assessment as the primary outcome to be able to pool data (Cleeland *et al.* 2010, Cavaletti *et al.* 2013).

Secondary Outcome Measures

All other measures were considered as secondary endpoints.

Common secondary endpoints were:

1. Overall Survival (OS)
2. Progression- Free Survival (PFS)
3. Time to Progression (TTP)
4. Tumor Response (TR)
5. Quality of Life (QoL)
6. Other adverse effects according to WHO or NCI-CTCAE, including treatment-related death
7. Other outcomes such as functional tests, pain scales or pain questionnaires.

2.3 Criteria for exclusion of studies

All non- randomized trials, case- control trials, cohorts and observational studies were excluded. Additionally, animal trials and pediatric studies were not considered for this SR. As described above published abstracts were not included but mentioned.

2.4 Search methods

2.4.1 Electronic search

For the systematic search keywords for prevention, therapy and disease patterns were collected and a search strategy was designed. It was developed by apl. Prof. Dr. med. Karin Jordan, Dr. med. Franziska Jahn from the Clinic of Internal Medicine, the Methodologist Mrs. PD Dr. rer. nat. Susanne Unverzagt from the Institute of Medical Epidemiology, Biostatistics and Informatics and by the doctoral candidate. All search strategies are attached in the appendices (see appendix 1). The following electronic data bases were searched:

1) Cochrane Central Register of Controlled Trials (CENTRAL) of Cochrane Library up to May 2014. Search performed by PD Dr. rer. nat. Unverzagt on April 4th 2013.
2) MEDLINE via PUBMED up to May 14th 2013. Search performed by doctoral candidate Juliane Beckmann. Updated up to May 2014.
3) MEDLINE via Ovid up to April 24th 2013. Search performed by PD Dr. rer. nat. Unverzagt.

2.4.2 Hand search

In addition, reference lists were scanned to ensure no trials were overseen and hand search was performed in *The Lancet Oncology, Journal of the National Cancer Institute, Annals of Oncology, Supportive Care in Cancer and Journal of Clinical Oncology* from January 2010 up to June 2014 (Juliane Beckmann).

2.4.3 Identification of relevant studies

First studies found based on the search strategy were selected by title. After exclusion of inapplicable studies full text articles of probably eligible studies were ordered. The remaining RCTs were searched by three independent evaluators (apl. Prof. Dr. med. Karin Jordan, Dr. med. Franziska Jahn, Juliane Beckmann) on the basis of their abstract or full text regarding the in- and exclusion criteria. Studies were organized by substance, prevention and therapy. Disagreements about inclusion were resolved by discussion in the team. The PRISMA flow chart (see chapter 4.2, figure 2) shows the procedure of the selection process.

2.5 Data extraction and grading

2.5.1 Extracting data

Study data was extracted into tables using the template of the S3 – guideline for supportive therapies in cancer care (Juliane Beckmann). The studies were separated in two different tables: one for prevention, the other for therapy of CIPN.
Tables were afterwards checked by three members of the working group (Prof. Dr. med. Karin Jordan, Dr. med. Franziska Jahn, PD Dr. rer. nat. Susanne Unverzagt). Discrepancies about data extraction were resolved by team consensus. The table template included following items:

- General information: authors, publication date, full text or part of existing review. Due to clarity, throughout the thesis, in the tables and forest plots, citations are shortened to the name of the first author and the year of publication, e.g. Albers et al. 2011 is abbreviated to Albers 2011.
- Trial characteristics: study design, single- vs. multi-center trial, study arms, number of randomized patients, country, duration
- Patients: sort of cancer or indication, age, sex, chemotherapy: dose, number of cycles, regimen
- Interventions and control: dose and sequence of chemotherapy, placebo or no therapy
- Outcomes: endpoints as described in the trial, sorted by categories (primary and secondary outcome)
- Main result: primary outcome: CIPN (any assessment) and relevant toxicities (in case of significant differences between groups)
- Main result: secondary outcomes (OS, PFS etc.)
- Financial support of the trial
- Grading: levels of evidence evaluated with CEBM and SIGN levels, reasons for down-grading (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014)

2.5.2 Grading of studies

This review being developed in the context of the S3- guideline for supportive therapy in cancer care, grading evidence of the included trials and reviews is needed to make a recommendation whether the anti-neurotoxic agent should be used in clinical practice. Patients and clinicians must weigh out advantages and disadvantages of therapies. The

decision is not only influenced by the quality of evidence of the studies. The strength of a recommendation is also affected by the confidence that the effect estimates are correct, their magnitude is likely and by the balance between desirable and undesirable consequences of the investigated treatments. In addition, alternative treatment options influence the final recommendation (Guyatt *et al.* 2011a).

We used centre for evidence-based medicine- levels (CEBM) and Scottish Intercollegiate Guidelines Network- levels (SIGN) for grading the level of evidence (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

CEBM levels for RCTs and SRs can be graded with level 1a to 1b and level 2a to 2b.

Level 1a stands for a SR with homogeneity among the included high quality trials. Individual RCTs with narrow confidence interval are rated 1b.

SRs of either retrospective cohort studies or untreated control groups in RCTs are graded 2a. Level 2b describes individual cohort studies or low quality RCT with a weak follow-up (OCEBM Levels of Evidence Working Group 2011). A detailed table of the CEBM-levels is given in appendix 2.

Using SIGN, high quality meta-analyses, SRs of RCTs with a very low risk of bias are graded 1++. Level 1+ is standing for well-directed RCTs and meta-analyses with a low risk of bias, while level 1- describes reviews and randomized trials with a high risk of bias (Scottish Intercollegiate Guidelines Network 2014, see appendix 3).

Grading was performed by PD Dr. rer. nat. Susanne Unverzagt and Juliane Beckmann. Different ratings were discussed and resolved by consensus.

2.5.3 Risk of bias

Assessing the risk of bias of the included references and grading their quality is important to judge about the level of evidence of the trial. It is needed for making recommendations and to ensure a high quality of SRs and evidence-based guidelines. A low risk of bias confirms that the estimated effects and their magnitude are valid (Guyatt *et al.* 2011d).

Trials should be well-conducted. But in clinical practice, it is often difficult to perform high standards concerning every methodical issue. Studies often fail in methodical correctness concerning allocation concealment, blinding, time to follow-up or intention-to-treat (ITT) (Guyatt *et al.* 2011d).

According to the Cochrane Handbook, the following sources of bias should be considered. By means of *Review Manager* it is possible to conduct *Risk of Bias Summaries.* They picture an overview of the included references and their risk of bias. Three gradations can be made.

When the method was described properly and exactly, a low risk of bias can be assumed. This is pictured with a "plus" in green color. Assuming a high risk of bias, a red "minus" is pictured and when risk of bias is unclear, a yellow "question mark" is shown.

The following categories for a possible risk of bias should be considered (Higgins and Green 2011, Review Manager 2014)

- Random sequence generation - to prevent selection bias. Participants should be included randomly. Random sequence should be generated by computer, throwing coins or using random number tables. The procedure should be specified in the study protocol. If performed so, a low risk of selection bias can be assumed. If not described properly, but authors claimed the trial as randomized, we describe the risk of bias as unclear.
- Allocation concealment- to prevent selection bias. The allocation of the subjects into the groups should not be foreseeable to neither participants nor assessors. Low risk of selection bias can be assumed when e.g. sealed envelopes were used.
- Blinding of participants and personnel- to prevent detection bias. It ensures constant and un-biased behavior of the participants. Low risk of detection bias can be expected when either no blinding was intended or when it is unlikely that the blind has been broken.
- Blinding of outcome data- to prevent detection bias. It ascertains unbiased outcome assessment. Low risk can be assumed when assessors are properly blinded or when no blinding was intended. Especially for subjective outcomes blinding of the outcomes is important.
- Incomplete outcome data might induce attrition bias. Missing data can bias the statement of an intervention. Low risk can be assumed, when effect sizes are plausible and when all results are presented for the pre-described methods.
- Selective reporting might induce publication bias. Risk is assumingly low when the study protocol is available and all pre-planned outcomes are presented. Next to questioning publication bias by methodical approach based on the Cochrane handbook, it can also be calculated by *Review Manager* (Higgins and Green 2011, Review Manager 2014).

Publication bias is the statistical biased presentation of data, mainly to find in scientific journals and papers to publish significant or "positive" effects of interventions. These results are unrepresentative for the study population and even wrong treatment regimens can result

from publication bias. Thus, it must be investigated when grading quality of evidence and considered when pooling effects. Especially for meta-analysis it is crucial to evaluate possible bias because its results can be distorted considerably (Rothstein *et al.* 2005, Guyatt *et al.* 2011c).

For exclusion and presentation of publication bias, studies found can be displayed in a funnel plot. A funnel plot is a scattered plot of the effect estimates of the single included studies against some measure of each study's size or precision (Higgins and Green 2011). Hereby the effect of treatment on the abscissa is plotted against the variance of the study on the ordinate. Assuming the effects and variables are uncorrelated, a symmetric picture of an "inverted funnel" can be displayed. The precision of the calculated effect of the intervention raises as the study has a large sample size. Thus, large studies scatter narrow around the graph.

The "inverted funnel" can be seen if the chance of publication bias is low.

Though, funnel plots can only be created if more than ten studies can be included. Due to the small number of studies processing an issue we relinquished funnel plots and were not able to proof the existence of publication bias statistically.

It cannot be ruled out that this meta-analysis contains publication bias (Higgins and Green 2011) .

2.6 Data analysis and synthesis

2.6.1 Measuring treatment effects

In the included studies, often dichotomous data types were evaluated. For example when measuring CIPN with NCI-CTCAE: Did peripheral sensory neuropathy of a certain grade appear or not. To compare the study groups, we estimated risk ratios (RRs). The RR represents the quotient of the probability of a certain disease in an exposed group compared to the probability in a group without that intervention. RRs can't be applied in retrospective case-control-studies since the ratio of cases and controls is determined by the investigator. In that case, an odds ratio (OR) is able to approach the risk ratio. The OR is the quotient of the chance that an exposition is present in sick people divided through the chance that the exposition is present in healthy people.

Nevertheless in many RCTs ORs are presented instead of RRs. Since it is easier to interpret, we decided to calculate RRs, even though the study used OR as an estimator (Sauerbrei and Blettner 2009).

When events in the intervention group are significantly less common than in the control group, then RR and OR (and their 95% confidence intervals) are less than 1.0.

If the converse holds true, these values will be greater than 1.0. When RR or OR equal 1.0, no difference between the study groups can be detected (Kvas 2005).

In some RCTs nerve amplitudes and nerve conduction velocities were assessed at baseline, during and after chemotherapy and their means were calculated. These measures are continuous. For calculating confidence intervals (CI) and comparing groups, mean differences (MDs) and their CIs were estimated. A MD could be calculated if all studies in the meta-analysis used the same scale. If different scales or questionnaires are used, it is of advantage to apply the standardized mean difference. Since we only pooled data using the same assessment tool, we decided to calculate MDs (Kvas 2005, Scott 2008, Szumilas 2010).

An MD of "0" means no difference of the metric value between the groups. If the MD is "<0" the metric value in the intervention group is smaller than in the control group.

All treatment effects were displayed in their 95% CI.

All calculations were performed with the program Review Manager 5.3 provided by the Cochrane Collaboration RevMan 5.3 (Review Manager 2014). Results were reported according to Preferred Reporting Items for Systematic Reviews and Meta- analyses (PRISMA) (Moher *et al.* 2009).

2.6.2 Meta-analysis and forest plots

The treatment effects of comparable studies which reported the same outcomes were eligible for comparison and could be pooled in meta-analysis. To be able to pool data, we decided to summarize data independent of the length of their follow-up period and pooled treatment effects; e.g.: CIPN was assessed via NCI-CTCAE in one study after six month, in another after eight month, then data was summarized to NCI-CTCAE six to eight month after treatment start.

Data synthesis was performed using Review Manager 5.3 for creating forest plots (Review Manager 2014).

The plots enable illustration of the effect measure with their 95% CI of every single study and the pooled effects and their 95% CIs. Additionally, heterogeneity can be displayed.

Reading forest plots, the following should be considered:

The effect of every included study is squared on a horizontal axis. The size of the square represents the weighting of the study in meta-analysis. The more precise the effect of the intervention is estimated, or in other words the narrower the 95% CI interval is, the more the RCT is weighted. The data synthesis follows the Mantel- Haenszel method described after Cochran, Mantel and Haenszel (Mantel and Haenszel 1959). The Mantel- Haenszel- test allows the comparison of two groups assessed with dichotomous or continuous outcome measures. It

is applied for a randomized study design, when allocation to the group is not controllable but when covariates can be controlled. It takes the risk of confounding into account which is probable in clinical trials (McDonald 2014, LaMorte and Sullivan 2016).

The confidence interval is pictured as the horizontal axis through the square. The diamond below the itemized studies shows the results of the pooled treatment effects. Its left and right edge represent the borders of the calculated 95% CI (Higgins and Green 2011).

On the left, the effect of every single study and the pooled data is readable. If no difference between the study groups (intervention and control) exists then meta-analysis is resulting at the value of one or calculating mean differences of zero. To find a statistical significant difference the 95% CI must be excluding the value of one (or for MD zero). This "line of no effects" is displayed as a vertical line (Higgins and Green 2011).

Since only few studies were included in meta-analyses and it is unlikely that these studies are homogenous, the random- effects model was used. In contrast to the fixed- effects model, the random- effects model assumes that the unobserved heterogeneity is not correlating with one of the variables. The random effects model should be applied when for example collection of information is performed from various medical centers or at different points of time (Taylor 2010).

2.6.3 Handling missing data

For analyzing and displaying continuous data in Forest Plots via Review Manager the mean and its standard deviation are needed. If these data are missing, it is possible to calculate those with the formula according to Hozo 2005. This formula is only valid by approximation and for a number of cases less than 25 (formula 1 und 2; x = mean, m=median, a = minimal value, b = maximum value, s= standard deviation) (Hozo *et al.* 2005).

$$\mathbf{x} = \frac{\boldsymbol{a} + \mathbf{2}\boldsymbol{m} + \boldsymbol{b}}{\mathbf{4}}$$

Formula 1: Calculation of the mean

$$\boldsymbol{s}^{\mathbf{2}} = \frac{\mathbf{1}}{\mathbf{12}}\left(\frac{(\boldsymbol{a} - \mathbf{2}\boldsymbol{m} + \boldsymbol{b})^{\mathbf{2}}}{\mathbf{4}}\right) + (\boldsymbol{b} - \boldsymbol{a}^{\mathbf{2}})$$

Formula 2: Calculation of the standard deviation

2.6.4 Assessing heterogeneity

Trying to conflate data by comparing different studies in a SR or meta-analysis, one must necessarily expect certain diversity in studies. Ideally, results of RCTs that shall be combined and compared in the meta-analysis should be contracted in the same way, under equal conditions and to the same experimental protocols. Of course, this ideal is usually not met. Heterogeneity is an expression of that condition (Higgins *et al.* 2003, Fletcher 2007).

So called *clinical heterogeneity* can be explained by different assessors, places, patients, gender, different types of cancers or outcomes.

Methodical heterogeneity includes different study designs, the diverse of statistical tests or bias.

Statistical heterogeneity displays the percental deviation between the effect's estimates in the different studies which cannot be explained by chance. It results from clinical and methodical heterogeneity.

Statistical heterogeneity or short I^2 was calculated to decide whether treatment effects could be summarized in meta-analysis. The value of I^2 can range from 0 % to 100 %. Following Cochrane Collaboration's handbook heterogeneity of 0 to 40% is considered as not important, 30 to 60% as moderate, 50-90% as substantial and 75 to 100% as considerable heterogeneity (Curwen 1971, Higgins *et al.* 2003, Fletcher 2007, Higgins and Green 2011). Taking into account that heterogeneity is present, the random effects model is suitable for meta-analysis.

It involves an assumption that the effects being estimated in the different studies are not identical, but follow some dispersion.

This procedure follows the recommendations of GRADE for quality grading of inconsistent study situation (Atkins *et al.* 2004, Guyatt *et al.* 2011a, Higgins and Green 2011, Guyatt *et al.* 2012).

2.7 From evidence to recommendation

This procedure followed the recommendations of GRADE for quality grading of inconsistent study situation (Atkins *et al.* 2004, Guyatt *et al.* 2011a, Higgins and Green 2011, Guyatt *et al.* 2012).

GRADE helped to estimate the importance of outcomes, to evaluate the level of evidence, to define reasons for down or up grading and forming a recommendation and to avoid bias (Atkins *et al.* 2004).

In conclusion, the results of this SR are based on RCTs only, which is securing a high quality of evidence compared to SRs including retrospective studies or case studies.

Still, the results are limited by several issues (Guyatt *et al.* 2011a). The restricted number of studies existing for some of the supportive therapies and the small sample sizes result in imprecision (Guyatt *et al.* 2011b).

In addition, inconsistent treatment effects with a lack of comparability, selective reporting and the inclusion of patients from a more generalized indication may limit the strength of evidence in SRs and reduce their reliability (Guyatt *et al.* 2011c, Guyatt *et al.* 2011d, Guyatt *et al.* 2012). Following GRADE, we tried to reduce bias and avoid adverse impact on the quality of this SR.

As described above this dissertation thesis is part of the S3- guideline "Supportive Therapy in cancer Patients". At this point, a short description of the procedure from completed search, identification, extraction, grading and analysis of data to the finished recommendation shall follow.

First evidence tables were compiled from October 2013 to January 2014. The tables included the extracted literature and served as basis for the CIPN working group where they were consented. If possible and reasonable, meta-analysis was performed. It was conducted by the doctoral candidate and checked by Prof. Dr. med. Karin Jordan, Dr. med. Franziska Jahn and PD Dr. rer. nat. Susanne Unverzagt. The forest plots were presented to the other members of the neurotoxicity working group and consented (May to June 2014).

On the basis of the analyses, from August to October 2014, recommendations were developed and background texts were created in the CIPN working group.

These recommendations were presented to the whole guideline team in the consensus meeting in April 2015. Verbalizations were refined and all suggestions were taken on vote. In the long version of the guideline the recommendations are presented with level of evidence, grade of recommendation and result of the voting.

As mentioned priorly, the level of evidence for every single study was determined based on CEBM and SIGN levels. Both grading strategies can be found in appendix 2 and 3.

In the German-speaking world the grades of recommendation summarized in table 4 are established. They are modified after the Strength-of-Recommendation Taxonomy (SORT) and the Agency for Healthcare Research and Quality (AHCPR) (Ebell *et al.* 2004, AHRQ 2014).

Table 4: Grades of recommendation (Ebell *et al.* 2004)

Grades of recommendation	Description	Expression
A	Strong evidence to support recommendation, according to levels of evidence Ia and Ib (CEBM)	"We recommend..."
B	Moderate evidence to support recommendation, according to levels of evidence II and III (CEBM) or extrapolation of level I, when studies interest differs from interrogation	"We suggest..."
0	Poor evidence to support recommendation, according to levels of evidence IV (CEBM) or extrapolation of level II and III, when no clinical studies of good quality were available	"could"

The level of consent is based on the following framework (see table 5).

Table 5: Levels of consent

Level of consent	Prozentuale Zustimmung
Strong consent	> 95% of the eligible voters
Consent	> 75 – 95% of the eligible voters
Majority approval	> 50 – 75% of the eligible voters
Dissent	< 50% of the eligible voters

In the following, on the example of alpha-lipoic-acid the presentation of level of evidence, grade of recommendation and results of the expert's voting can be seen (see table 6).
The expert's voting displays the following numbers: Level of consent, number of eligible voters, number of dismissals and abstentions and the the percental consent.

Table 6: Presentation of grade of recommendation, level of evidence and results of voting on the example of alpha-lipoic- acid (ALA)

	Evidence- based recommendation
Grade of recommendation A	Prophylaxis with ALA should not be performed.
Level of Evidence **1b**	De novo: Guo 2014 (Guo *et al.* 2014)
Voting	Strong consent; 37-0-3; 100 %

3 Results

In the following section results of the search, the studies and meta-analyses are displayed and summarized.

3.1 Search results

Electronic search was performed in three data bases in April and May 2013 (see appendices, appendix 1). Using the search strategies as described above 1241 references were identified (490 in PUBMED, 501 in MEDLINE, 250 in CENTRAL). Nine hundred-sixty records were screened by title and abstract after duplicates were removed. Eight hundred and three references were excluded due to irrelevance for the issue. Hundred and fifty-seven full text articles were ordered and read critically. In- and exclusion criteria were applied. Ninety-six studies were considered as inappropriate and 58 studies plus three SRs were included in this SR. Additionally, hand search identified 89 references.

Twenty-nine references could finally be considered for meta-analyses. Not all RCTs could be included for the following reasons:

- for many substances only one RCT was eligible for inclusion
- more than one study existed but no common outcome measure was applied, so treatment effects could not be pooled
- statistical heterogeneity, measured by I^2 was higher than 75% and following Cochrane's Handbook estimating overall effect measures should not be performed (Higgins and Green 2011)

All working steps are displayed in the PRISMA flow chart (see figure 2)(Moher *et al.* 2009).

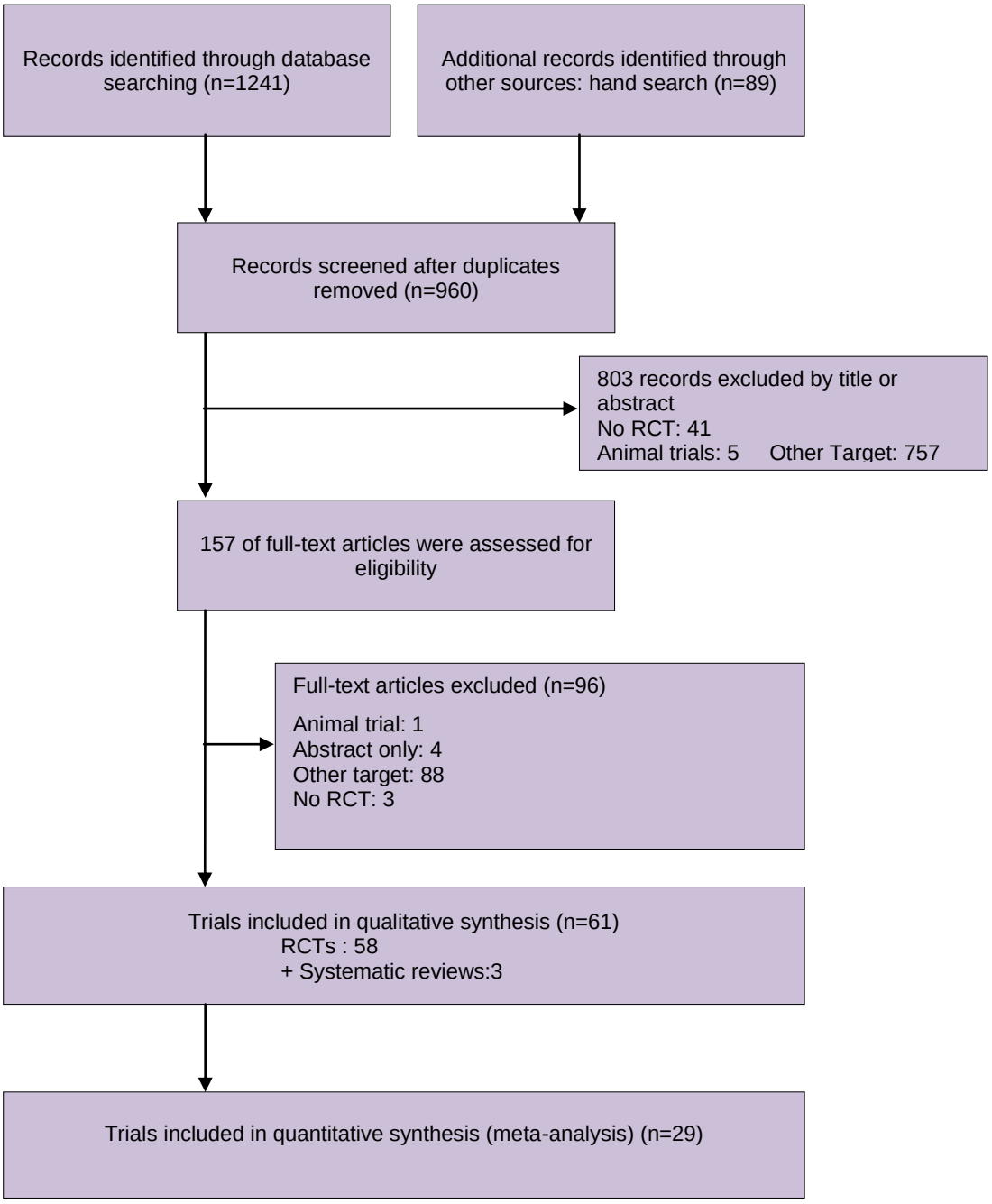

Figure 2: PRISMA flow chart for illustration of reference selection process
(Moher *et al.* 2009)

3.2 Included studies

Fifty-eight RCTs and three SRs (Albers *et al.* 2011, Wu *et al.* 2012, Wen *et al.* 2013) were included. A total of 3015 patients received a platinum compound- based chemotherapy regimen in studies investigating the prevention of chemotherapy-induced neurotoxicity. We identified seventeen RCTs and one SR including 1469 patients which were treated with cisplatin. Another seventeen trials and three SRs investigated the prevention of CIPN in 1546 patients receiving oxaliplatin. In an additional RCT either cisplatin or oxaliplatin was given to

243 patients (Guo *et al.* 2014). And one other study investigated preventive options in 207 participants with neurotoxicity induced by cisplatin, oxaliplatin, carboplatin, paclitaxel or a combination of these (Kottschade *et al.* 2011). Exact numbers of treatment groups were not reported.

Additionally, twelve RCTs and one SR with a total of 1362 patients treated with taxanes or the combination of paclitaxel and carboplatin were identified. Furthermore, one trial including patients treated with paclitaxel and/or cisplatin met inclusion criteria (Argyriou *et al.* 2005). Two trials with 180 patients who were treated with vinca alkaloid- based regimens met our pre-defined inclusion criteria (Koeppen *et al.* 2004, Kottschade *et al.* 2011). One trial explored prevention of CIPN in 222 participants receiving bortezomib (Moreau *et al.* 2011).

In addition, we included six RCTs investigating therapeutic options for CIPN in 801 participants who have been receiving any kind of neurotoxic chemotherapy. The following table gives an overview of the included studies and their references (see table 7).

Table 7: Overview of references included

All citations can be found in the list of citations. In the following, or naming the studies, they are abbreviated with: first author year.

	Included Reviews and Studies	Number of patients included
1 Prevention of CIPN		
1.1Platinum derivatives		
1.1.1 Cisplatin		
	Albers 2011:	SR: 1198
	Argyriou 2005 Also included patients treated with cisplatin	35
	Bogliun 1996	54
	Cascinu 1995	50
	Gandara 1995	214
	Hovestadt 1992	18
	Kemp 1996	242
	Pace 2003	47
	Planting 1999	74
	Roberts 1997	196
	Schmidinger 2000	20
	Smyth 1997	151
	Van Gerven 1994	42
	Van-der-Hoop 1990	55
References not included in Albers 2011:		
	Bodnar 2008	40
	Cassidy 1998	50
	Colombo 1995	33
	Guo 2013 Also included patients treated with oxaliplatin	243

Table 7: Overview of references included

All citations can be found in the list of citations. In the following, or naming the studies, they are abbreviated with: first author year.

	Included Reviews and Studies	Number of patients included
1 Prevention of CIPN		
1.1Platinum derivatives		
1.1.1 Cisplatin		
	Kottschade 2011 Also included patients treated with oxaliplatin, paclitaxel, carboplatin or combination	207
	Pace 2010	108
	Rick 2001	40
1.1.2 Oxaliplatin		
	Albers 2011:	SR: 166
	Argyriou 2006	40
	Cascinu 2002	52
	Ishibashi 2010	33
	Lin 2006	14
	Milla 2009	27
	Wen 2012	1170 (RCT: 162)
	Chay 2010	27
	Ishibashi 2010	33
	Grothey 2011	102
	Wu 2012	1238 (RCT: 255)
	Chay 2010	27
	Ishibashi 2010	33
	Grothey 2011	102
	Kono 2009/11	89
References not included in a SR:		
	Afonseca 2013	34
	Durand 2011	48
	Guo 2013	243
	Kottschade 2011 Also included patients treated with oxaliplatin, paclitaxel, carboplatin or combination	207
	Loprinzi 2014	353
	Nishioka 2011	45
	Von Delius 2006	36
	Wang 2007	86
	Zhang 2012	80
	Zhu 2013	120
1.2 Taxanes: Paclitaxel, Paclitaxel + Carboplatin, Docetaxel		
	Albers 2011	SR: 225
	Kanat 2003	38
	Lorusso 2003	187
	Argyriou 2005 Also included patients treated with cisplatin	35
	Davis 2005	117
	De Vos 2005	90

Table 7: Overview of references included
All citations can be found in the list of citations. In the following, or naming the studies, they are abbreviated with: first author year.

	Included Reviews and Studies	Number of patients included
1 Prevention of CIPN		
1.2 Taxanes: Paclitaxel, Paclitaxel + Carboplatin, Docetaxel		
	Gelmon 1999	40
	Goreishi 2012	69
	Hershman 2013	409
	Hilpert 2005	72
	Kottschade 2011	207
	Leal 2014	185
	Loven 2009	67
	Leong 2003	60
	Kaku 2011	29
1.3 Vinca alkaloids: Vincristin		
	Koeppen 2004	150
	Van Kooten 1992	30
1.4 Protease inhibitor: Bortezomib		
	Moreau 2011	222
2 Therapy of CIPN		
	Smith 2013	231
	Barton 2011	208
	Kautio 2008	44
	Rao 2008	131
	Rao 2007	115
	Hammack 2002	57

3.3 Excluded studies

Of the 157 screened full text articles, 96 were excluded. Reasons for exclusions are presented in the PRISMA flow chart (see figure 2). One trial was investigating CIPN in rats (Arrieta *et al.* 2011) and was therefore excluded. In four cases abstracts only were available (Rudolph 2001, Gamelin *et al.* 2008, Dong *et al.* 2010, Nakamura *et al.* 2015) and we excluded the abstracts due to lack of information and reporting bias. Eighty-eight studies were not directly targeting the efficacy of anti-neurotoxic agents in prevention or therapy of CIPN. Three studies were excluded due to a lack of randomization.

3.4 Presentation of results

Using electronic data base search a range of studies could be identified. Reference's characteristics, grading and results of meta-analysis are displayed as follows. Forest plots were illustrated when studies were comparable. Detailed information about the studies are presented in the tables of evidence (see appendix 4 and 5).

3.4.1 Prevention of CIPN

Acetylcysteine (ACC)

Characteristics and grading evidence

One RCT for the prevention of oxaliplatin-induced neurotoxicity with 1200 mg oral n-acetylcysteine was identified (Lin *et al.* 2006), which was included in the Cochrane review of Albers 2011 (Albers *et al.* 2011).

A total of 14 participants were randomized to acetylcysteine (five participants) or placebo (nine participants). Patients received chemotherapies in dosages of up to 85 mg/m^2 oxaliplatin biweekly, in addition weekly 5-fluoruracil (5-FU) and leukovorine were applied. Dosages were reduced to 75% if grade 2- neurotoxicity appeared and discontinued at the appearance of grade 3-4 neurotoxicity. Median follow-up was 18 months (Lin *et al.* 2006).

This pilot trial using oral n-acetylcysteine (n-ACC) for the prevention of CIPN was very small-sized. Method of randomization, allocation concealment and blinding was unclear. Not all electro-physiologic results were reported for both study arms and treatment effects were not presented quantitatively. Full neurological examination was performed before start, during and after therapy, but results were not described. For the reason of small size, reporting bias and missing study data, this RCT was graded with 2B- (CEBM) and 1-(SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

After twelve cycles, the incidence of neurotoxicity was less in the intervention than in the placebo arm (grade 1: 4 of 5 patients (80%) vs. 9/9 pat. (100%) (RR 0.79; 95% CI 0.49 to 1.28)/ grade 2: 1/5 pat. vs. 8/9 pat (RR 0.23; 95% CI 0.04 to 1.32) /grade 3: 0/5 pat. (0%) vs. 3/9 pat. (33%)(RR 0.24, 95% CI 0.01 to 3.86). Electro-physiologic data were only reported for the intervention arm (Lin *et al.* 2006).

Acetyl-L-Carnitine (ALC)

Characteristics and grading evidence

One RCT with 409 participants was identified to investigate the benefit of acetyl-L-carnitine (ALC) (208 patients) for preventing CIPN compared to placebo (201 patients) (Hershman *et al.* 2013). The intervention group received 500 mg ALC daily. Patients suffered from breast cancer and received a taxane- based CTX. Dosages of paclitaxel varied from 80 mg/m^2 to 175 mg/m^2 for up to six cycles. Docetaxel was given with 75 mg/m^2 for up to six cycles, as well.

This large RCT of Hershman 2013 was randomized, but method of allocation and randomization was not described. Blinding of participants and time to follow-up were adequate. An intention-to-treat (ITT) analysis was performed. The quality of evidence of this trial was graded 1B (CEBM) and 1+ (SIGN) (OCEBM Levels of Evidence Working Group 2011).

Results

Primary endpoint of the study was patient's assessment with the neurotoxicity section of Functional Assessment of Cancer Therapy for Taxanes (FACT-Ntx) at 12 weeks. Secondary endpoints were NCI-CTCAE criteria, FACT- Ntx at 24 weeks and fatigue measured with the Functional Assessment of Chronic Illness Therapy (FACIT).

A more than five points lowering in FACT-Ntx score was considered as clinically relevant. At 12 weeks no significant difference between the groups was detected. The score was 5.2 counts lower compared to baseline in the ALC group and 4.5 counts in the placebo arm.

A multivariate linear regression after 24 weeks showed a trend towards more patient-reported neuropathy in the ALC arm (MD 1.8 counts, 95%CI to 0.4 to 3.2)(Hershman *et al.* 2013).

No statistically significant difference could be detected assessing neuropathy of any grade with NCI-CTCAE (RR 0.90; 95%CI 0.71 to 1.15).

ACTH- Analogue: Org 2766

Characteristics and grading evidence

Our search identified six RCTs with a total of 489 patients to evaluate the potential protective effects of Org 2766 in patients treated with neurotoxic agents. The four trials for cisplatin (van der Hoop *et al.* 1990, Hovestadt *et al.* 1992, van Gerven *et al.* 1994, Roberts *et al.* 1997) were included in the Cochrane review of Albers 2011 (Albers *et al.* 2011). Two trials investigated the effect of Org 2766 in patients treated with vincristine.

Cisplatin trials were:

- Cisplatin for ovarian cancer (129 Org 2766 treated participants, 63 treated with low dose Org 2766 at 2 mg/kg and 66 with high dose Org 2766 at 4 mg/kg and 67 control participants)(Roberts *et al.* 1997).
- Cisplatin for testicular and adeno-carcinoma (19 Org 2766 treated participants and 23 placebo)(van Gerven *et al.* 1994).
- Cisplatin for ovarian cancer (7 Org 2766 treated participants and 11 placebo)(Hovestadt *et al.* 1992).

- Cisplatin for ovarian cancer (17 low dose Org 2766 (0.25 mg/m^2 treated participants, 16 high dose Org 2766 (1 mg/ m^2) and 22 placebo (van der Hoop *et al.* 1990).

Vincristine trials:

- Vincristine for Hodgkin and Non-Hodgkin-Lymphoma (75 Org 2766 treated participants and 75 placebo) (Koeppen *et al.* 2004)
- Vincristine for Hodgkin and Non-Hodgkin-Lymphoma (13 Org 2766 treated participants and 15 placebo) (van Kooten *et al.* 1992).

The Org 2766 regimens largely varied among trials from 0.25 to 4 mg/kg. Org 2766 was applied subcutaneously in all six trials. In three trials Org 2766 treated patients were stratified in two arms, one low-dosage and one higher-dosage Org 2766 arm (van der Hoop *et al.* 1990, Hovestadt *et al.* 1992, Roberts *et al.* 1997). Cisplatin was given up to nine cycles, dosages varied from 75 up to 100 mg/m^2.

Vincristine was administered at cumulative dosages from 8 to 32 mg in two to eight courses (Koeppen *et al.* 2004) or at a maximum dose of 2 mg, repeatedly over six courses (van Kooten *et al.* 1992). Figure 3 shows the characteristics and risk of bias of the included references.

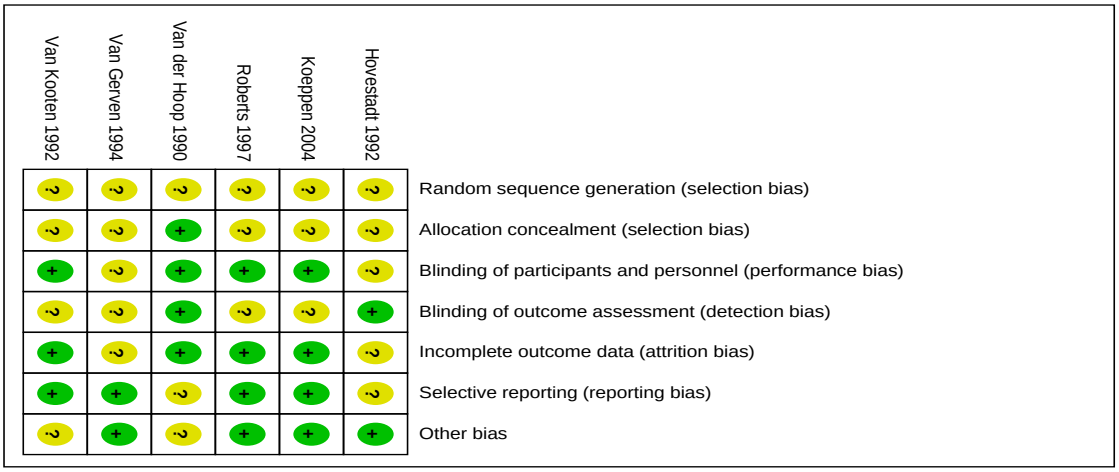

Figure 3: Org 2766- Risk of bias summary
Note: + indicates criteria were met, ? indicates not reported, no detail, uncertain if the criteria were met, - indicates criteria were not met

All but one cisplatin trials were graded with CEBM level 2B- and SIGN level 1- due to small sample size and deemed secure methodical descriptions (van der Hoop *et al.* 1990, Hovestadt *et al.* 1992, van Gerven *et al.* 1994). One trial had an adequate sample size and was graded 1B- and 1+ (Roberts *et al.* 1997). The later vincristine trial received level 1B- and 1+, as well (Koeppen *et al.* 2004). The study of Van Kooten 1992 was graded with level 2B- and 1- due to very small sample size and significant differences in median age between the study groups (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

Vibration- perception threshold (VPT) was measured from the second metacarpal bone of each hand in four trials with the Virbraton II (van der Hoop *et al.* 1990, Hovestadt *et al.* 1992, van Gerven *et al.* 1994, Koeppen *et al.* 2004). One trial just stated no significant difference in VPT but did not report standard deviation or range, thus it could not be illustrated in the forest plot (Koeppen *et al.* 2004). One study only performed a descriptive analysis but no VPT values were reported (Hovestadt *et al.* 1992). The RCT of Van Kooten 1992 measured VPT on left first toe and did not find significant changes between study groups (MD: -0.28; 95% CI -0.64 to 0.08). The largest cisplatin trial did not detect any significant change in VPT between the study groups, no matter if patients received 2 or 4 mg Org 2766 (Low dose group: MD: 0.25; 95% CI -0.32 to 0.82) , (high dose group: MD: 0.71; 95% CI -0.08 to 1.50) (Roberts *et al.* 1997). In the study of van-der-Hoop, also a low dose and a high dose Org2766 group received the study drug at either 0.25 mg/ml or at 1 mg/ml per square meter. The treatment with 0.25 mg/ml showed a significant and clinically relevant protective effect (MD -3.56; 95% CI -4.46 to -2.66). Likewise, high dose Org2766 showed a beneficial effect on CIPN compared to placebo (MD: -4.99; 95% CI -5.82 to -4.16).

The overall effect measure MD of -1.62 µv (95% CI -3.34 to 0.09 µv) actually slightly favors the intervention with considerable statistical heterogeneity (I^2=97%) of treatment effects (details shown in figure 4). Following Cochrane's Handbook, the data shouldn't be pooled (Higgins and Green 2011).

Another primary endpoint was neuropathy and pain- free interval and feeling of numbness. No statistical significant differences were found (Koeppen *et al.* 2004). The trial of Van Kooten 1992 found significant differences in total number of complaints about autonomic dysfunction (1 versus 12) and feeling of numbness in hands or feet (9 versus 29) between the intervention and control group, respectively. As secondary endpoints tumor response rates were collected in the two vincristine trials (van Kooten *et al.* 1992, Koeppen *et al.* 2004). Thirty-two of 73 (23,4%) versus 27 of 74 (20%) patients experienced complete response (CR) in the Org2766 group and placebo group, respectively (Koeppen *et al.* 2004). In neither of the trials a significant difference in tumor response (TR) was found. Quality of life questionnaires were applied in one trial but did not show any differences between study groups (Koeppen *et al.* 2004).

Of note, Org 2766 is not available in German- speaking world.

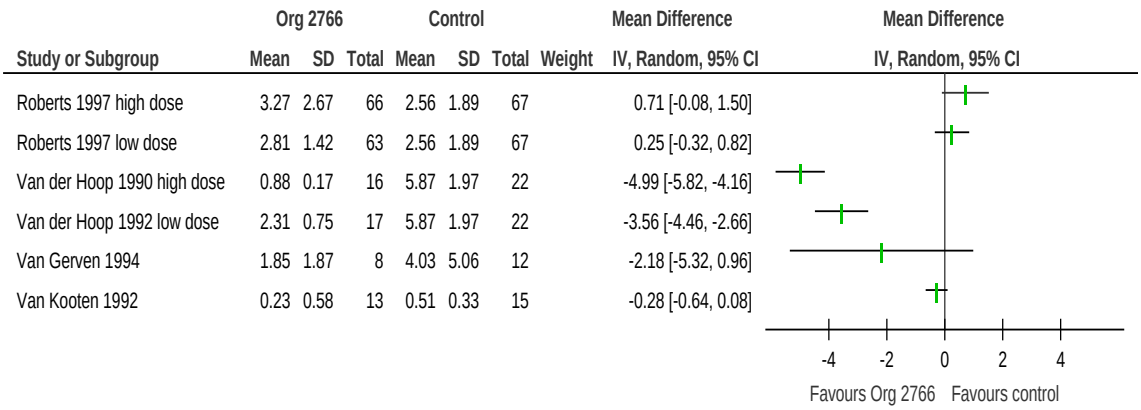

Figure 4: Forest plot for comparison of median difference of VPT in µv at 3-5 months. Org 2766 arm versus control.

Alpha-lipoic acid (ALA)

Characteristics and grading evidence

One study investigating the effect of oral alpha-lipoic acid in the prevention of cisplatin or-oxaliplatin induced CIPN was identified (Guo *et al.* 2014). A total of 243 participants was stratified into six groups according to their prior platinum exposure having received

1) no cisplatin;

2) dosages of less than 399 mg/m^2;

3) more than 400 mg/m^2 cisplatin;

4) no oxaliplatin;

5) less than 750 mg/m^2 or

6) receiving more than 750 mg/m^2 oxaliplatin.

One hundred and twenty-two patients were allocated into the intervention group receiving 600 mg alpha-lipoic acid three times daily for 24 weeks, whereas placebo was given to 121 participants (Guo *et al.* 2014).

The trial was described as randomized but the method of randomization and allocation concealment remained unclear. This RCT has a double-blinded design. The primary outcomes were patient reported. No electro-physiologic assessment was performed.

Study data at 36-weeks and 48-weeks time point were not evaluated due to the high number of drop outs in both groups. The main limitation of this trial was that only 34 of 122 patients (28%) in the intervention arm and 36 of 121 patients (30%) in the control arm could be examined at 24 weeks time point. Main reasons given were patient withdrawal and patient non-compliance. Thus, the study was closed preliminary. Tumor response rates were not

shown completely. Authors concluded that the effect of ALA could not be estimated due to lack of power, early closing and missing data (Guo *et al.* 2014).
Therefore, the trial was graded level 2B- (CEBM) and 1- (SIGN) (OCEBM Levels of Evidence Working Group 2011, Guo *et al.* 2014, Scottish Intercollegiate Guidelines Network 2014).

Of note, it was not possible to find out how many patients received cisplatin or oxaliplatin.

Results

Neurotoxicity was measured with NCI-CTCAE and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group -Neurotoxicity (FACT/GOG Ntx) scale. As described above only few of the participants were eligible for analysis at 24 weeks. No significant difference in adverse events between the study arms was detected (Guo *et al.* 2014). Differences in patient reported outcomes were not found, either (NCI-CTCAE grade 1/2: RR 1.06; 95% CI 0.82 to 1.37; grade 3-4: RR: 0.64; 95% CI 0.16 to 2.46).
Additionally, results from the timed functional tests such as time to button a six-hole button shirt or a 50 foot walk at fastest speed and Brief Pain Inventory (BPI) were assessed. All functional tests showed no significant differences between the groups at 24 weeks. As a secondary endpoint, other toxicities than CIPN were assessed with NCI-CTCAE as well. Treating physicians gathered for Tumor Response data, but did not detect any differences between the study groups (Guo *et al.* 2014).

Amifostine

Characteristics and grading evidence

Nine trials with 843 patients investigating amifostine for the prevention of CIPN were identified all together.
In three trials with 356 participants, two of them included in Albers 2011 (Kemp *et al.* 1996, Planting *et al.* 1999), study participants were treated with cisplatin-based regimens. Paclitaxel or paclitaxel plus carboplatin were administered in six trials (487 patients), as well, two being part of Albers 2011 (Kanat *et al.* 2003, Lorusso 2003).

- Cisplatin, paclitaxel, ifosfamide, followed by high-dose carboplatin, etoposide and thiopeta for germ cell tumors (20 amifostine treated patients, 20 patients receiving no treatment) (Rick *et al.* 2001, Albers *et al.* 2011).
- Cisplatin for head and neck cancer (37 amifostine treated patients, 37 patients receiving placebo) (Planting *et al.* 1999).
- Cisplatin for ovarian cancer (122 amifostine treated patients, 120 patients receiving no treatment) (Kemp *et al.* 1996, Albers *et al.* 2011).

- Paclitaxel and carboplatin for non-small-cell lung cancer (19 amifostine treated patients, 19 patients receiving no treatment) (Kanat *et al.* 2003, Albers *et al.* 2011).
- Paclitaxel and carboplatin for ovarian cancer (94 amifostine treated patients, 93 patients receiving no treatment)(Lorusso 2003, Albers *et al.* 2011).
- Paclitaxel and carboplatin for ovarian cancer (45 amifostine treated patients, 45 patients receiving no treatment) (De Vos *et al.* 2005).
- Paclitaxel and carboplatin (TC) and partly with additional epirubicin (TEC) for ovarian cancer (37 amifostine treated patients, 34 patients receiving placebo) (Hilpert *et al.* 2005).
- Paclitaxel and carboplatin plus radiotherapy for unresectable non-small-cell lung cancer (30 amifostine treated patients, 30 patients receiving placebo)(Leong *et al.* 2003).
- Paclitaxel for breast cancer in palliative situation (20 amifostine treated patients, 20 patients receiving no treatment) (Gelmon *et al.* 1999).

Dosages of amifostine varied from 500-910 mg/m^2 given prior to application of chemotherapy as intravenous infusion.

Cisplatin dosages varied largely, dependent on the individual cancer and regimen applied. In one study cisplatin was combined with paclitaxel and carboplatin as other potential neurotoxic agents (Rick *et al.* 2001).

Paclitaxel was often administered in combination with carboplatin. Both agents are known to be neurotoxic. Dosages of paclitaxel varied from 175 mg/m^2 to 250 mg/m^2, carboplatin with an area under the curve (AUC) from five to six per cycle. In only one trial paclitaxel was applied as mono therapy (Gelmon *et al.* 1999).

Method of randomization was adequate in two trials (Leong *et al.* 2003, Lorusso 2003) and allocation concealment in only one trial (Lorusso 2003).

Investigating amifostine as potential agent to ameliorate CIPN, most included trials compared amifostine to no treatment. Only two trials had patient and observer blinding (Leong *et al.* 2003, Hilpert *et al.* 2005).

Detection bias was probable in all trials except in the study of Leong 2003.

Follow-up was adequate in all trials. Trials of Leong 2003 and Gelmon 1999 had small sample sizes.

Study data were missing in Hilpert 2005. Here, it was reported that only 66 patients were eligible for toxicity analyses but neither reasons for drop-out of patients nor the final number of remaining participants in the groups was reported. For further information see the risk of bias summary (see figure 5).

Six trials were graded 2B (CEBM) and 1- (SIGN) due to lack of blinding, small sample size, high number of drop outs and lack of methodical reporting (Kemp *et al.* 1996, Gelmon *et al.* 1999, Planting *et al.* 1999, Rick *et al.* 2001, Kanat *et al.* 2003, Leong *et al.* 2003, Hilpert *et al.* 2005). The trial of DeVos 2005 and Hilpert 2005 were graded 1B- (CEBM) and 1+ (SIGN). One study with low risk of bias was graded 1B and 1+ (Lorusso 2003).

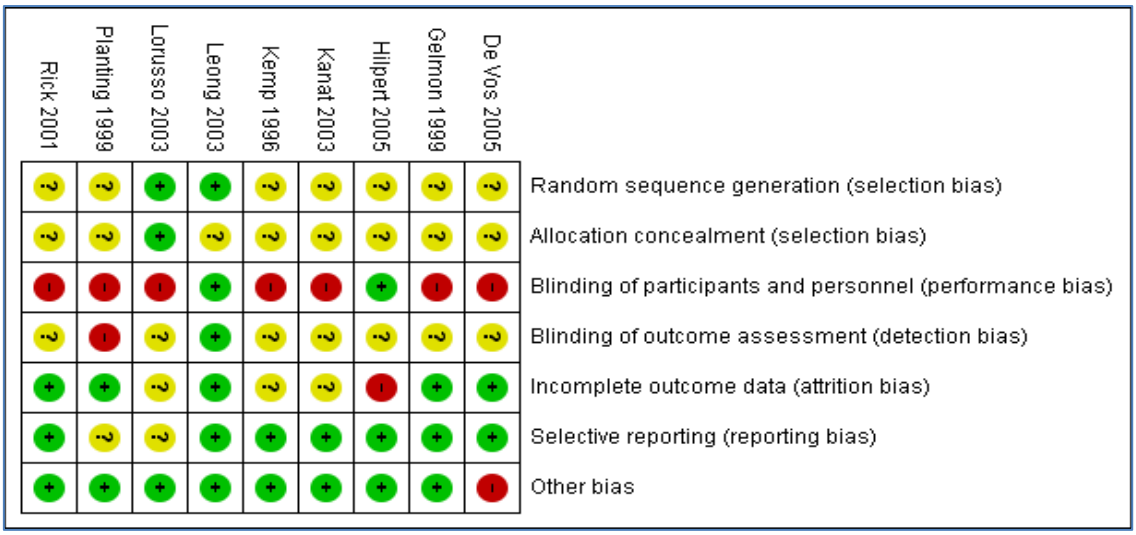

Figure 5: Amifostine- Risk of bias summary
Note: + indicates criteria were met, ? indicates not reported, no detail, uncertain if the criteria were met, - indicates criteria were not met

Results

Five studies used NCI-CTCAE as an endpoint. In Hilpert 2005 comparing NCI-CTCAE of all grades a borderline protective effect of amifostine was found (RR 0.80, 95% CI 0.64 to 1.00). Though, neither the trial of DeVos 2005 (RR 0.95; 95%CI 0.79 to 1.13) nor the trial of Leong 2003 (RR 1.07, 95% CI 0.94 to 1.22) affirmed this result. Gelmon 1999 concluded that amifostine had no protective effect in the prevention of CIPN, as well. The incidence of neurotoxicity (NCI-CTCAE grade 1-3) was 100% (20 of 20 pat.) in both arms (RR 1.0; 95% CI 0.91 to 1.10).

The study of Kemp 1996 investigating cisplatin-induced CIPN found marginal significant differences between the groups favoring the protective effect of amifostine (RR 0.81; 95%CI 0.66 to 1.00) (see figure 6).

The overall treatment effect could not be calculated due to substantial statistical heterogeneity between the studies (I^2=79%). Due to the high heterogeneity, we analyzed subgroups of the different chemotherapeutics (for details see figure 6). Of note, comparing the studies investigating paclitaxel and amifostine, a substantial statistical heterogeneity (I^2=75%) has to be taken into account.

Two studies assessed neurotoxicity via vibration perception threshold (VPT) measured on both hands. The values were not comparable since baseline values were not reported and again numbers of patients eligible were missing. Both trials detected less subclinical neurotoxicity in the intervention groups (Planting *et al.* 1999, Hilpert *et al.* 2005).

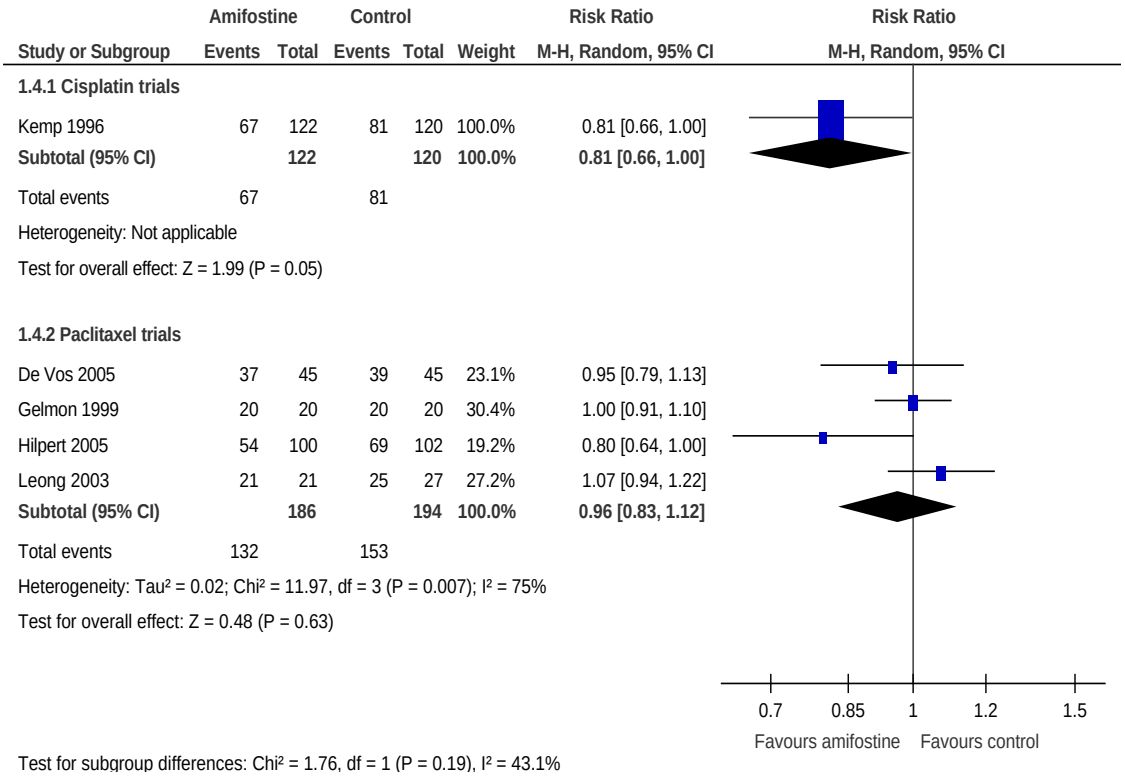

Figure 6: Forest plot for comparison of CIPN NCI-CTCAE (all grades) amifostine arm versus control.

A secondary endpoint was quality of life assessed in two trials using EORTC questionnaires. DeVos 2005 and Hilpert 2005 found no significant differences between the study groups.

Amifostine caused more nausea, vomiting and occasional hypotension reported in DeVos 2005 and in Gelmon 1999. The study of Hilpert 2005 detected a disadvantage of patients receiving amifostine with regard to dyspnoea, infection, nausea and vomiting.

None of the studies reported differences in survival rates or progression of disease. No interference of amifostine with antitumor efficacy of chemotherapy agents was detected.

Calcium and Magnesium

Characteristics and grading evidence

We identified five RCTS with a total of 655 participants investigating the preventive effect of calcium and magnesium supplements (Ca/Mg) against oxaliplatin- induced peripheral neuropathy (Chay *et al.* 2010, Ishibashi *et al.* 2010, Grothey *et al.* 2011, Hochster *et al.* 2014,

Loprinzi *et al.* 2014). One additional study researched the efficacy of magnesium only supplements in 40 patients treated with cisplatin- based regimens (Bodnar *et al.* 2008).

In former meta-analyses various studies were included. The studies excluded in this review shall be described in more detail. For the study of Dong 2010 and Gamelin 2008 no full publication was available and thus they did not meet eligibility criteria (Gamelin *et al.* 2008, Dong *et al.* 2010). The study of Dong 2010 was only fully published in Chinese. For Gamelin 2008, only a letter to the editor with preliminary results was found.

In the following an overview of the included studies shall be given. All patients were treated with oxaliplatin with a dose ranging from 85 to 130 mg/m^2 and suffered from colorectal cancer. Both, curative and palliative settings were considered. Ca/Mg infusions consisted of 850 to 1000 mg calcium gluconate and 720 to 1500 mg magnesium sulfate.

- Hochster 2014 = the CONcePTrial (Combined Oxalipatin Neurotoxicity Prevention Trial) with 140 patients in a 2x2 design, the trial was designed to explore the possible benefit of intermitting administration of oxaliplatin compared to continuous application. Ca/Mg was given additionally and compared with placebo, though its efficacy was no pre-defined endpoint of the study. 70 patients received Ca/Mg before and after CTX and 69 patients a placebo (Hochster *et al.* 2014).
- Loprinzi 2014 with 353 patients in a cross-over design, Ca/Mg before and after CTX (n=118); placebo before and after CTX (n=119); Ca/Mg before CTX and after CTX placebo (n=116) (Loprinzi *et al.* 2014).
- Grothey 2011 with 102 patients, Ca/Mg before and after CTX (n=50); placebo before and after CTX (n=52) (Grothey *et al.* 2011).
- Chay et.al. 2010 with 27 patients; Ca/Mg before and after CTX (n=13); placebo before and after CTX (n=14) (Chay *et al.* 2010).
- Ishibashi 2010 with 33 patients; Ca/Mg before and after CTX (n=17); placebo before and after CTX (n=16). This RCT is included in the SR of Albers 2011 (Ishibashi *et al.* 2010, Albers *et al.* 2011).

Two SRs pooled the results of re- and prospective studies investigating the efficacy of Ca/Mg (Wu *et al.* 2012, Wen *et al.* 2013).

The SR of Wu 2012 included a Japanese retrospective study which also investigated the efficacy of Goshajinkigan (GJG), a Japanese herb. To clarify the confusing titling of literature concerning GJG a short explanation shall follow. The study of Kono et al. , included in Wu 2012, was published in 2011 (in the SR of Wu 2012, it is named Kono 2009). It was of retrospective nature and included four treatment groups with Ca/Mg or GJG or a combination of both.

To our knowledge, a later RCT of Kono et al., also with confusing publication data, was fully published in English language in 2013. This trial investigated GJG only and will be described later on (Kono *et al.* 2011, Kono *et al.* 2013).

The review of Wen 2013 slightly favored the use of Ca/Mg whereas the review of Wu 2012 discouraged its use (Wu *et al.* 2012, Wen *et al.* 2013)

Furthermore, an RCT investigated the protective efficacy of magnesium subcarbonate and magnesium sulphate. The study of Bodnar 2008 included 40 patients with epithelial ovarian cancer treated with cisplatin and paclitaxel. Primary endpoint of the study was the nephroprotective effect of magnesium supplementation (Bodnar *et al.* 2008).

The exact method of randomization process and allocation concealment was described in one of the studies (Ishibashi *et al.* 2010). Adequate blinding of patients and personnel was performed in five studies (Chay *et al.* 2010, Ishibashi *et al.* 2010, Grothey *et al.* 2011, Loprinzi *et al.* 2014).

Most of the trials had inadequate sample size with a lack of statistical power. Three trials were closed early due to the preliminary results of the CONCEPT study published in 2007 by Hochster and Grothey *et al.* which detected a lower anticancer efficacy when oxaliplatin was combined with calcium and magnesium infusions (Chay *et al.* 2010, Ishibashi *et al.* 2010, Grothey *et al.* 2011).

Only the trial of Loprinzi 2014 had adequate power (Loprinzi *et al.* 2014). The total number of drop-outs was less than ten percent in all trials except in the study of Chay 2010 in which results for the frequency of CIPN were only reported for patients who entirely finished the study.

An intention to treat analysis was performed in three trials (Chay *et al.* 2010, Grothey *et al.* 2011, Hochster *et al.* 2014, Loprinzi *et al.* 2014)(see figure 7). The SRs of Wen 2012 and Wu 2012 were graded with 2A (CEBM) 1- (SIGN). since they included retrospective studies. The trial of Grothey 2011 was graded level 1B (CEBM)and 1+ (SIGN). Three studies were graded with level 2B (CEBM) and 1- (SIGN) (Chay *et al.* 2010, Ishibashi *et al.* 2010, Hochster *et al.* 2014). The latest study of Loprinzi 2014 received CEBM level 1B and SIGN 1+. The RCT of Bodnar 2008 was graded 2B (CEBM) and 1- (SIGN) due to methodical limitations.

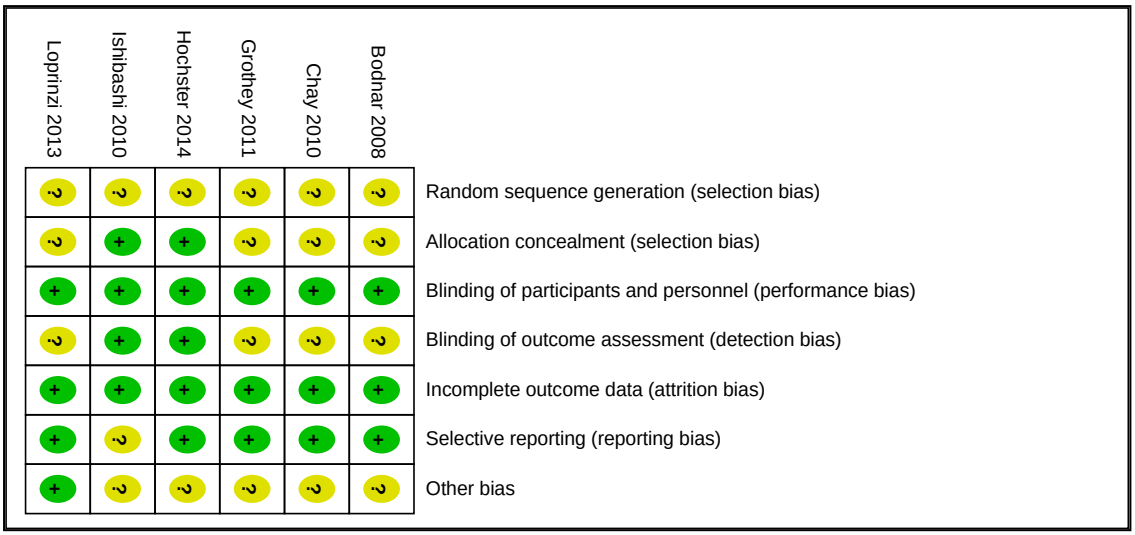

Figure 7: Ca/Mg- Risk of bias summary
Note: + indicates criteria were met, ? indicates not reported, no detail, uncertain if the criteria were met, - indicates criteria were not met

Results

All included trials used NCI-CTCAE scores for assessment of CIPN and could thus be considered for meta-analysis. It was possible to pool data for neurotoxicity assessed with NCI-CTCAE all grades for two small-sized studies (Chay *et al.* 2010, Ishibashi *et al.* 2010) and for ≥grade 2 for four studies (Chay *et al.* 2010, Ishibashi *et al.* 2010, Grothey *et al.* 2011, Hochster *et al.* 2014, Loprinzi *et al.* 2014) (see figures 8 and 9).

The results of the trial of Chay 2010 did not state a significant difference (RR 0.79, 95% CI 0.54 to 1.15), neither the trial of Ishibashi 2010 did (RR 1.07, 95% CI 0.90 to 1.26). The overall effect was not significant with a RR of 0.95 (95% CI 0.69 to 1.32) with substantial statistic heterogeneity of I^2=62 % (Chay *et al.* 2010, Ishibashi *et al.* 2010).

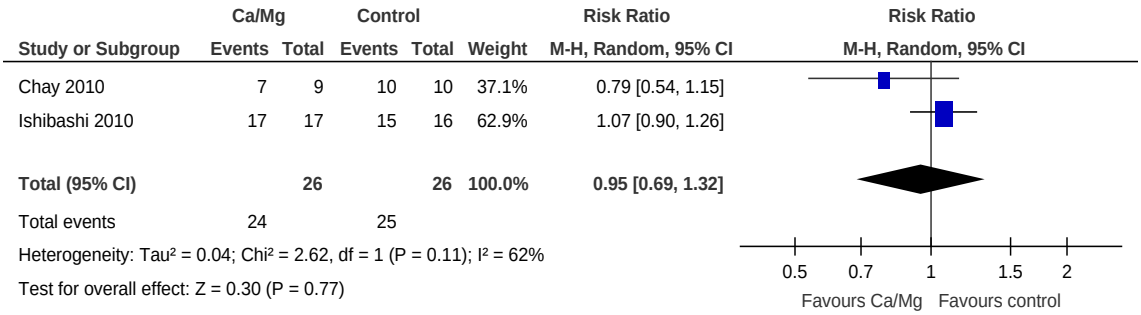

Figure 8: Forest plot for comparison of CIPN NCI-CTCAE (all grades) Ca/Mg arm versus control.

Grothey 2011 discovered a significant difference in favor of the placebo when assessing no or grade 1 CIPN (RR 1.35, 95% CI 1.03 to 1.78) (Grothey *et al.* 2011).

Measuring grade 2 or higher CIPN, in the newly published results of the CONCePT trial of Hochster 2014 no significant benefit of Ca/Mg infusions was found (RR 0.67; 95% CI 0.35 to 1.30) (Hochster *et al.* 2014).

Concomitant, Loprinzi 2014 detected no significant differences in grade 2 or higher neurotoxicity assessed with NCI-CTCAE (RR 0.98; 95% CI 0.76 to 1.27) (Loprinzi *et al.* 2014).

One of 17 patients suffered from neurotoxicity grade 2 or 3 in the intervention group and one of 16 participants in the placebo arm (Ishibashi *et al.* 2010: RR 0.94; 95% CI 0.06 to 13.82).

In Grothey 2011, eleven of 50 in the Ca/Mg arm and 21 of 52 patients in the placebo arm experienced CIPN grade 2 or higher (RR 0.54; 95% CI 0.29 to 1.01) (Grothey *et al.* 2011).

The overall effect did not show any significant difference in favor of Ca/Mg (RR 0.81; 95% CI 0.60 to 1.11). Heterogeneity was low (I^2=20%).

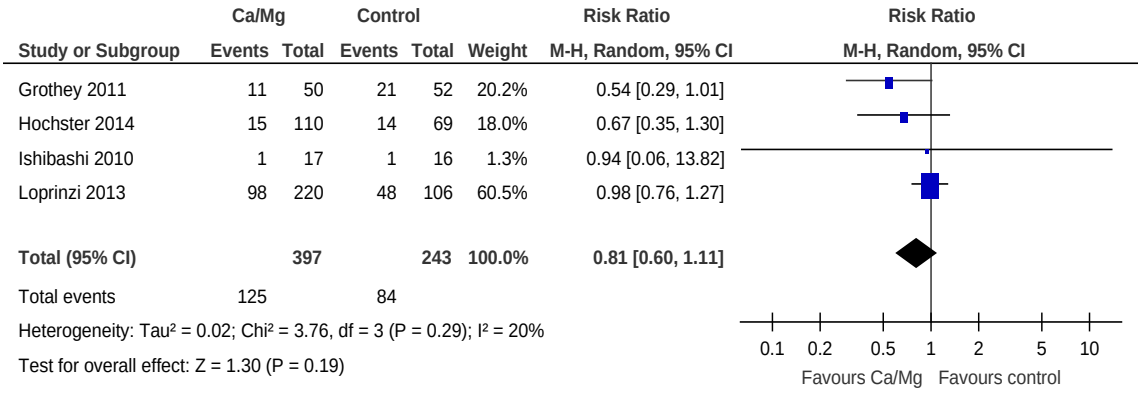

Figure 9: Forest plot for comparison of CIPN NCI-CTCAE (≥ grade 2) Ca/Mg arm versus control

Another primary outcome applied in four references was neurotoxicity assessed with oxaliplatin-specific scale (OSS) or DEBT-NTS, which can be compared (Chay *et al.* 2010, Ishibashi *et al.* 2010, Grothey *et al.* 2011, Loprinzi *et al.* 2014). But Loprinzi 2014 only showed the time to neuropathy grade 2 or higher measured with OSS and thus could not be considered for meta-analysis.

The trial of Grothey 2011 found a significant difference between groups favoring Ca/Mg infusions. Fourteen of 50 participants experienced grade 2 or higher neurotoxicity in the intervention arm compared to 26 of 52 patients in the placebo arm (Grothey *et al.* 2011: RR 0.56; 95% CI 0.33 to 0.94). In the trial of Chay 2010 four of nine versus three of ten participants had ≥grade 2 CIPN (RR 1.48; 95% CI 0.45 to 4.90) (Chay *et al.* 2010). In Ishibashi 2010 no significant difference between the study groups was found, either (RR 1.25; 95% CI 0.74 to 2.13) (Ishibashi *et al.* 2010). The estimated overall effect was neither favoring Ca/Mg nor the control with a RR of 0.93; 95% CI 0.49 to 1.80. Heterogeneity was substantial (I^2=64%) (for details see figure 10).

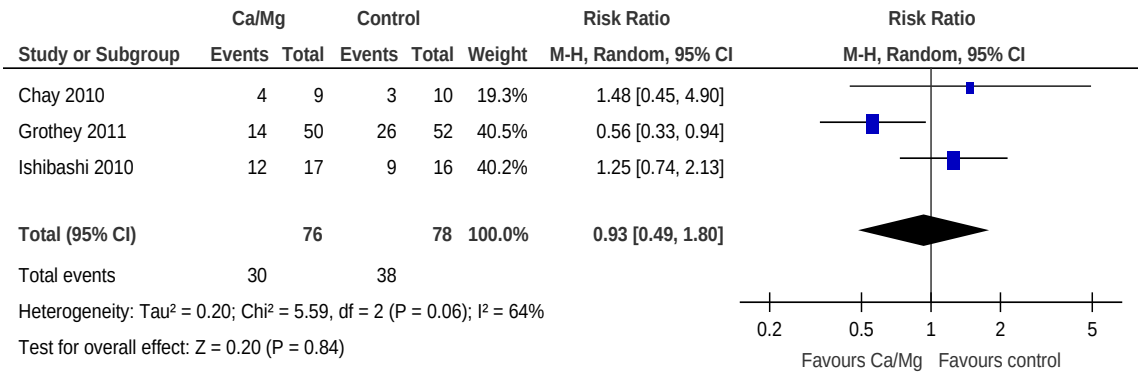

Figure 10: Forest plot for comparison of OSS Ca/Mg arm versus control

As secondary endpoints, survival and tumor response rates were collected in two studies (Ishibashi *et al.* 2010, Hochster *et al.* 2014). After the interim analysis which showed a negative effect of Ca/Mg on TR, the final results of the CONcePT did not find a difference in tumor response. Results showed significantly longer time to treatment failure (TTF) for the intermittent oxaliplatin group compared to the continuous administration (Hazard Ratio (HR) 0.58, 95% CI 0.41 to 0.83). Ca/Mg infusions showed no effect on tumor response (Hochster *et al.* 2014).

Combined tumor response rates were 13 of 26 (50%) and 14 of 26 (54%) patients in the intervention versus control arm, respectively (Ishibashi *et al.* 2010: RR 0.93; 95% CI 0.55 to 1.57).

One trial assessed quality of life with EORTC-QLQ- CIPN but could not find any relevant differences between the study groups. No meta-analysis was conducted (Loprinzi *et al.* 2014).

Carbamazepine

Characteristics and grading evidence

One trial investigating the efficacy of carbamazepine in preventing oxaliplatin- induced peripheral neuropathy was included (von Delius *et al.* 2007). A total of 36 patients suffering from colorectal cancer participated in the trial. Nineteen patients were allocated to the intervention group and 17 patients to the no treatment arm. Chemotherapy consisted of oxaliplatin (85 mg/m^2), folinic acid and 5-fluor uracil. The number of treatment cycles depended on tumor response. The intervention group received carbamazepine six days before oxaliplatin with an initial dose of 200 mg, which was elevated stepwise up to a targeted plasma level of 4-6 mg per liter (von Delius *et al.* 2007).

Random sequence generation was performed but the method was not described in detail. Allocation concealment was adequate. The control group received no treatment. Blinding of outcome assessment was not described.

An intention to treat analysis was performed. Sample size was small and patient recruitment was finished early due to competing treatment protocols (von Delius *et al.* 2007).

The trial of Von Delius 2006 was graded with 2B (CEBM) and 1- (SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Of note, the RCT of Eckel 2002 was excluded, since the intervention was compared to a historical control group (Eckel *et al.* 2002).

Results

Neurotoxicity was assessed with an oxaliplatin-specific neurotoxicity scale designed by Levi. It grades symptoms as paraesthesia and dysaesthesia by intensity and duration (Lévi *et al.* 1994). The calculated RR for CIPN of all grades was statistically significant with 0.75 (95% CI 0.56 to 0.99).

In addition, vibration sense was measured with a standard tuning fork and deep tendon reflexes were examined. The results of these neurologic examinations were assembled in a sum score. Neurological examination showed increase of function but no significant difference between study groups.

Antitumor efficacy was a secondary endpoint. No complete response could be observed in any of the study arms. Partial response was found in three patients in the carbamazepine arm (16%; 95%; CI 4% to 38%) and in four patients in the control arm (24%; 95% CI 8% to 49%). Median progression-free survival was 6.0 months versus 7.2 months in carbamazepine and control group, respectively. No significant differences were detected.

Toxicities that might be caused by carbamazepine were dizziness, headache, nausea, mnemonic problems and optical hallucinations which disappeared after discontinuing carbamazepine. These phenomena were observed in two patients.

Chemotherapy was stopped early in four patients in the intervention arm and in three patients in the control arm, respectively (von Delius *et al.* 2007).

Diethyldithiocarbamate (DDTC)

Characteristics and grading evidence

One study investigating the effect of DDTC in prevention of cisplatin-induced chemotherapy met eligibility criteria (Gandara *et al.* 1995). This trial was part of the Cochrane review of

Albers 2011. A total of 214 participants with ovarian cancer, small cell and non-small cell lung cancer were included in the multi-center trial. Patients (n=106) randomized into intervention group were scheduled to receive 1.6 g/m^2 DDTC 15 min before application of cisplatin. Hundred and eight patients received placebo. One hundred ninety-five patients were eligible for final analyses. Cisplatin (100 mg/m^2) was applied in combination with etoposide or cyclophosphamide for six cycles (Gandara *et al.* 1995). Of note, DDTC is not available in the German- speaking world.

Randomization and allocation concealment methods were unclear. Subject blinding was adequate but observer and outcome assessor blinding inadequate. A large number of drop outs, 40 in the intervention arm and 72 in the placebo arm, were noted due to progressive disease or toxicity (Gandara *et al.* 1995, Albers *et al.* 2011).

The trial was rated 1B- (CEBM) and 1- (SIGN) due to methodical limitations and a high rate of drop outs (Gandara *et al.* 1995, OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

Neurotoxicity was assessed with NCI-CTCAE criteria. No significant difference in the incidence of neurotoxicity between the study arms was found (DDTC arm: 13/96 (13%); placebo arm: 12/99 (12%); RR 1.12; 95% CI 0.54 to 2.32) (Gandara *et al.* 1995).

Secondary endpoints were other toxicities, as well assessed with NCI-CTCAE and TR rates.
Only six of 96 patients (6%) in the DDTC arm completed chemotherapy, in the placebo arm 28 of 99 patients (28%) received all six cycles of cisplatin. Seventy-one of 96 patients (74%) in the DDTC arm compared to 40 of 99 (40%) in the control group withdrew early from the study (RR 1.83; 95% CI 1.40 to 2.39).

Significant differences in reasons for withdrawal were found in nephrotoxicity assessed with serum creatinine levels (DDTC arm: 0.71 mg/dL; placebo arm: 0.17 mg/dL; $p<0.001$).
DDTC related toxicities were flushing, transient hypertension and hyperglycemia. No interference with the antitumor efficacy of cisplatin was found. Response rates were collected for 195 patients. Forty-nine percent (47/96) of the patients treated with DDTC and 43% (43/99) in the placebo arm had a complete or partial response (Gandara *et al.* 1995).

Glutamate

Characteristics and grading evidence

One study from Israel was identified investigating oral glutamate for the prevention of paclitaxel and carboplatin-induced peripheral neuropathy. Sixty-eight participants suffering from ovarian cancer were scheduled to receive paclitaxel and carboplatin. Paclitaxel was administered over at least six cycles with 175 mg/m^2. Carboplatin was given at an area under the curve of six (Calvert's formula). Twenty-three patients were allocated to the intervention arm receiving capsules of 500 mg glutamate three times daily. The control group consisted of 20 patients receiving placebo instead of glutamate (Loven *et al.* 2009).

The method of randomization and allocation concealment was described and adequate. Blinding of patients and personnel and outcome assessment was also performed adequately. Sample size was small and no intention to treat- analyses was performed. Only 43 of the 67 initially randomized patients were evaluable for final analyses. The drop-out rate was high with 36 percent. No statistical analyses of differences between groups as age, performance status, cancer stage etc. was given (Loven *et al.* 2009). The trial of Loven 2009 was graded with 2B- (CEBM) and 1- (SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

Neurological evaluations were performed and questionnaires were given to participants to assess tactile, pain and vibratory perception. All results were summarized in a *Severity Score* showing the increase in grade of toxicity compared with baseline values for tingling, numbness, pain and strength. No significant differences were detected between the groups for tingling, numbness and loss of strength. Only for the symptom of pain a borderline significant difference was found. None of 23 patients and 6 of 18 patients experienced pain in the intervention and in the control group, respectively (RR 0.06; 95% CI 0.00 to 1.01). In addition, electro-physiologic studies did not show significant differences, either. In 30.4 % (7 of 23 pat.) in the glutamate group and 30% (6 of 20 pat.) in the placebo group a change favoring glutamate in electro- physiologic assessment was detected (RR 1.01; 95% CI 0.41 to 2.52) (Loven *et al.* 2009).

Two patients in the glutamate group experienced severe skin rash, while none did in the control group. No other secondary outcomes were included in analyses. Authors described a high drop- out rate of 36 % (Loven *et al.* 2009).

Glutamine

Characteristics and grading evidence

Only one trial was performed to investigate the preventive effect of glutamine against oxaliplatin- induced neurotoxicity (Wang *et al.* 2007). Eighty-six participants with metastatic colorectal cancer were scheduled to receive glutamine or no treatment. Forty-two patients received 15 g oral glutamine twice a day over one week starting simultaneous with oxaliplatin. Forty-four participants didn't have any supportive treatment.

Oxaliplatin was administered with 85 mg/m^2 plus folinic acid and 5- fluor uracil (Wang *et al.* 2007).

The method of randomization was not described and allocation concealment was inadequate. No blinding was performed and the control patients did not received any treatment. Blinding of outcome assessment was not described. Follow- up was adequate and outcome data was complete (Wang *et al.* 2007).

The RCT of Wang 2007 was graded with CEBM level 2B and SIGN level 1- (Scottish Intercollegiate Guidelines Network 2014).

Results

Neurotoxicity was assessed with NCI-CTCAE grades at baseline and after two, four and six cycles of treatment. In addition, in some cases electro-physiologic studies were performed. Grade 1 neurotoxicity was detected in seven of 42 patients (17%) in the glutamine group and in 17 of 44 participants (38%) in the control group after two cycles (RR 0.43; 95%CI 0.20 to 0.93). After six cycles though, no significant difference between the study groups could be detected. Grade 1-2 neurotoxicity was experienced by 17 of 42 patients (40%) and 18 of 44 participants (40%) in the intervention and control group, respectively (RR 0.94; 95% CI 0.57 to 1.57).

None of the patients in the glutamine arm and one in the control arm suffered from Grade 3-4 neurotoxicity after two cycles of oxaliplatin (RR 0.35; 95% CI 0.01 to 8.33). After six cycles a significant difference was found. Only five participants (12%) in the intervention group and 14 patients (32%) in the control arm experienced grade 3-4 toxicity (RR 0.37; 95% CI 0.15 to 0.95) (Wang *et al.* 2007).

In addition, interference with activities of daily life (ADL) such as functional impairment when opening jars and buttoning was assessed. Interference with ADLs were observed in seven of 42 patients (7%) and in 18 of 44 participants (41%) in the glutamine and control arm, respectively (RR 0.41; 95% CI 0.19 to 0.87).

As secondary endpoints survival rates were estimated. No significant differences were observed. Seventeen of 42 (40%) patients in the glutamine arm and 18 of 44 (41%) patients in the no treatment arm experienced partial remission (RR 0.99; 95% CI 0.59 to 1.65).

Complete response could be observed in five compared to three patients in glutamine and control arm, respectively (RR 1.75; 95% CI 0.44 to 6.85). Overall survival rates were 17.3 versus 18.6 months (p= 0.79).

Treatment related toxicities were assessed with WHO criteria. No significant differences in other toxicities were observed between the study groups (Wang *et al.* 2007).

Glutathione (GSH)

Characteristics and grading evidence

Eight trials with a total of 572 patients investigated the potential anti-neurotoxic effect of glutathione (GSH). Three hundred and eight participants in five trials, four of them included in Albers 2011, received cisplatin- based regimens (Cascinu *et al.* 1995, Colombo *et al.* 1995, Bogliun *et al.* 1996, Smyth *et al.* 1997, Schmidinger *et al.* 2000). Two trials, also part of Albers 2011,with 79 patients scheduled to receive oxaliplatin were included (Cascinu 2002, Milla *et al.* 2009). Only one large study investigated GSH in prevention of paclitaxel-induced CIPN (Leal *et al.* 2014). In the following an overview of the included trials is given:

- Cisplatin against non-small cell lung cancer or head and neck cancers (11 patients treated with GSH, 9 patients treated with placebo) (Schmidinger *et al.* 2000). Included in Albers 2011.
- Cisplatin against ovarian cancer (74 patients treated with GSH, 77 patients treated with placebo) (Smyth *et al.* 1997). Included in Albers 2011.
- Cisplatin against ovarian cancer (27 patients treated with GSH, 27 patients treated with placebo)(Bogliun *et al.* 1996). Included in Albers 2011.
- Cisplatin against gastric cancer (25 patients treated with GSH, 25 patients treated with placebo)(Cascinu *et al.* 1995) Included in Albers 2011.
- Cisplatin against ovarian cancer (16 patients treated with GSH, 17 patients receiving no treatment) (Colombo *et al.* 1995). Included in Albers 2011.
- Oxaliplatin against colorectal cancer (14 patients treated with GSH, 13 patients treated with placebo)(Milla *et al.* 2009).
- Oxaliplatin against colorectal cancer (26 patients treated with GSH, 26 patients treated with placebo) (Cascinu 2002). Included in Albers 2011.
- Paclitaxel against breast cancer (94 patients treated with GSH, 91 patients treated with placebo) (Leal *et al.* 2014).

- Dosages of cisplatin varied from 40 mg/m^2 up to 100mg/m^2 for six to nine courses. In the two oxaliplatin trials a maximum of 12 cycles of chemotherapy with a maximum dose of 1,200 mg/m^2 was administered. Paclitaxel was given at dosages from 80-200 mg/m^2 plus carboplatin (AUC 5-7) for at least 12 weeks.

Glutathione was given intravenously before chemotherapy at dosages of 1.5 up to 5 mg/m^2.

Randomization and allocation concealment were adequate in four trials (Cascinu *et al.* 1995, Smyth *et al.* 1997, Cascinu 2002, Leal *et al.* 2014). Accurate blinding of personal and subjects was done in three trials (Cascinu *et al.* 1995, Cascinu 2002, Leal *et al.* 2014). Method of blinding of outcome assessors was described adequately in three studies as well (Cascinu *et al.* 1995, Bogliun *et al.* 1996, Cascinu 2002).

Three studies included only a very small number of patients (Colombo *et al.* 1995, Schmidinger *et al.* 2000, Milla *et al.* 2009). ITT- analyses were performed in Cascinu 2002 and Schmidinger 2000.

Follow-up was adequate in all included trials. For details see the risk of bias summary (figure 11).

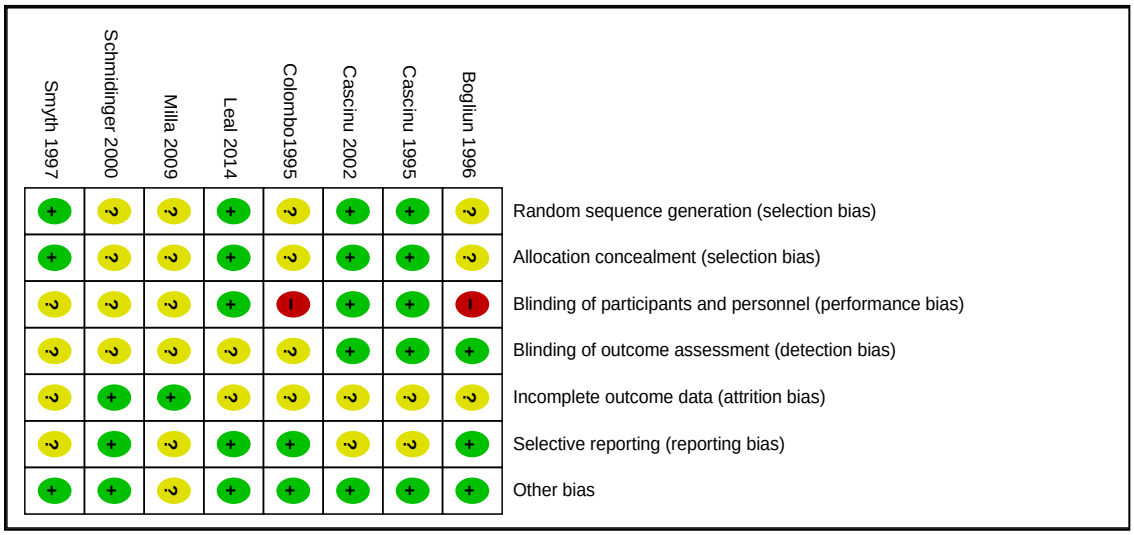

Figure 11: GSH- Risk of bias summary
Note: + indicates criteria were met, ? indicates not reported, no detail, uncertain if the criteria were met, - indicates criteria were not met

Four trials were graded with CEBM level 1B- and SIGN level 1- (Cascinu *et al.* 1995, Smyth *et al.* 1997, Cascinu 2002, Leal *et al.* 2014). Due to low quality of method and small sample sizes four trials were graded 2B (CEBM) and 1- (SIGN) (Colombo *et al.* 1995, Bogliun *et al.* 1996, Schmidinger *et al.* 2000, Milla *et al.* 2009).

Results

Primary outcome measures assessing CIPN were NCI-CTCAE criteria in four trials. In Smyth 1997 no significant difference between the study arms was detected. Twenty-nine of 74 patients (39%) suffered from cisplatin- induced neurotoxicity in the GSH arm and 38 of 77 (49%) in the placebo arm (RR 0.79; 95% CI 0.55 to 1.14). In Milla 2009 all participating patients developed peripheral neurotoxicity (RR 1.0; 95% CI 0.87 to 1.15). The other oxaliplatin trial detected neurotoxicity in nine of 21 (43%) in the GSH arm and in 15 of 19 patients (79%) in the control arm, favoring GSH (RR 0.54; 95% CI 0.31 to 0.94) (Cascinu 2002).

The trial investigating GSH for prevention of paclitaxel and carboplatin induced neurotoxicity found no statistically significant differences in the incidence of neurotoxicity between the study groups (RR 1.17; 95% CI 0.82 to 1.66) (Leal *et al.* 2014).

The overall effect showed no superiority of GSH compared to placebo, no statistical significance could be detected (RR 0.90; 95% CI 0.70 to 1.16). Heterogeneity of studies included in the comparison was substantial (I^2=61%). For further information see figure 12.

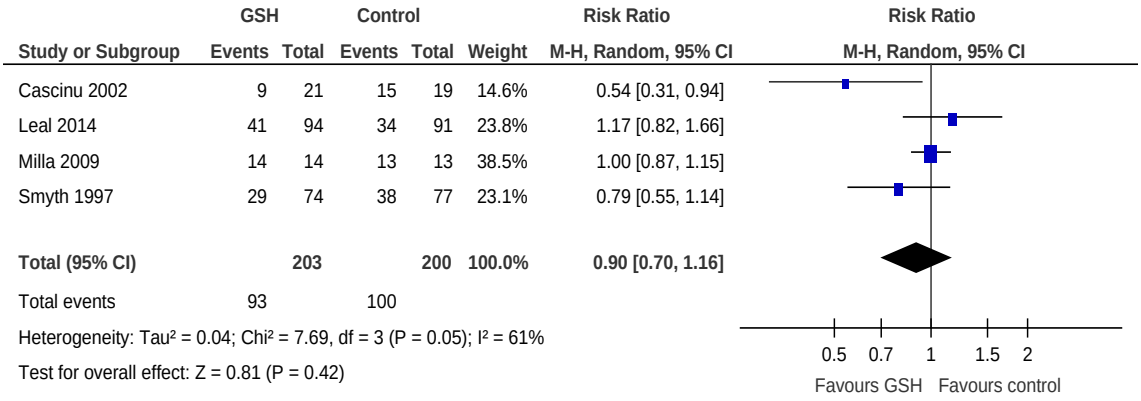

Figure 12: Forest plot for comparison of CIPN NCI-CTCAE (all grades) GSH arm versus control

Electro-physiologic measures were assessed in four studies (Cascinu *et al.* 1995, Colombo *et al.* 1995, Bogliun *et al.* 1996, Cascinu 2002). Four trials used sural SNAPs to estimate subclinical changes in nerve function. After calculating MDs no significant differences between the study groups could be detected (Cascinu 2002: MD -1.09 µv; 95% CI -4.45 to 2.27 µv; Bogliun 1996: no exact data; Cascinu 1995: MD 1.03 µv; 95% CI -1.59 to 3.65 µv; Colombo 1995: MD 2.07 µv; 95% CI -2.28 to 5.42 µv). The estimated overall effect was 0.74 µv (95% CI -1.02 to 2.50 µv) (Cascinu *et al.* 1995, Colombo *et al.* 1995, Bogliun *et al.* 1996, Cascinu 2002). For further information see figure 13.

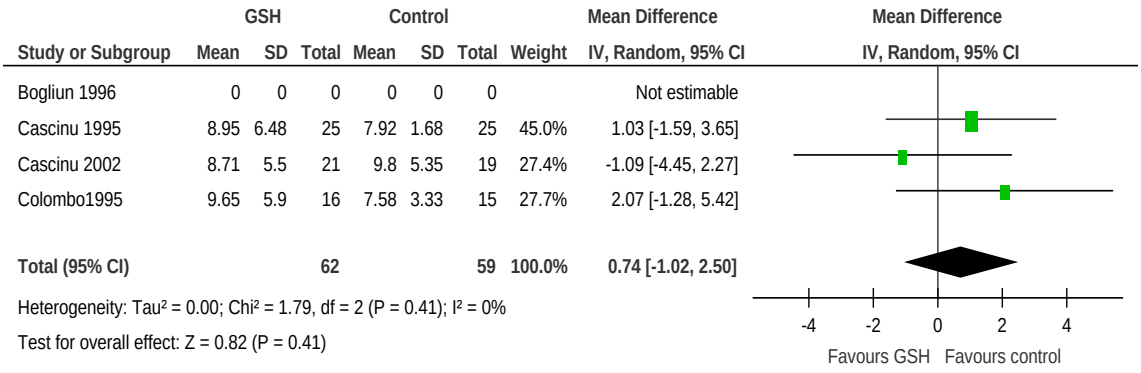

Figure 13: Forest plot for comparison of Sural SNAP Median GSH arm versus control

As secondary endpoints TR rates were evaluated in three trials, no significant differences were found (Colombo *et al.* 1995, Smyth *et al.* 1997, Cascinu 2002). PFS was 6.6 months versus 7.2 months in the GSH arm and the control arm, respectively (Schmidinger *et al.* 2000).

Two trials collected quality of life data, assessed with Hospital Anxiety and Depression Score (HADS), Rotterdam scores (Smyth *et al.* 1997) or EORTC-QLQ-CIPN (Leal *et al.* 2014). Depression scores showed less increase in score in the GSH arm compared to the control (increase GSH 0.8 vs. control 2.5, standard error 0.9). Anxiety scores showed no statistically significant difference. Changes in Rotterdam scores were detected in some items and an improvement of mood in the intervention arm. No exact data was given (Smyth *et al.* 1997). In assessment of EORTC no significant differences in quality of life were found (Leal *et al.* 2014).

Goshajinkigan

Characteristics and grading evidence

Goshajinkigan (GJG) is a traditional Japanese herbal medicine which has been used for treating diabetic neuropathy. A retrospective study showed beneficial effects of GJG on oxaliplatin-treated patients. The study included four treatment groups, receiving Ca/Mg infusion or GJG or a combination of both, and was also included in the SR of Wu 2012 (Kono *et al.* 2011). Another respective study included 73 patients receiving oxaliplatin-based CTX and also stated a preventive effect of GJG (Yoshida *et al.* 2013)

Three prospective trials investigating Goshajinkigan (GJG) were identified. A total of 167 patients were included. The latest trial, named the GONE study, had 89 participants in a prospective, randomized, placebo- controlled, double-blinded design. An abstract was already published in 2009 (Kono *et al.* 2013). Participants suffered from colorectal cancer and were scheduled to receive oxaliplatin-based FOLFOX 4 or mFOLFOX 6 regimens with oxaliplatin at 85 mg/m^2. The intervention group (44 patients) received GJG 7.5 g daily, starting on the day of chemotherapy over 26 weeks. Forty-five patients were allocated to the placebo group. Calcium

and Magnesium infusions were prohibited as long GJG was applied over 26 weeks, but not throughout the whole CTX (Kono *et al.* 2013).

The second trial investigating GJG for prevention of oxaliplatin-induced peripheral neuropathy included 45 patients (Nishioka *et al.* 2011). Treatment of colorectal cancer was oxaliplatin-based mFOLFOX6 scheme (oxaliplatin 85 mg/m^2). Twenty-two participants received 7.5 g GJG daily. Twenty-three patients had no treatment. Calcium and Magnesium infusions were prohibited (Nishioka *et al.* 2011).

Another trial evaluating GJG against paclitaxel/carboplatin- induced peripheral neuropathy in patients with endometrial or ovarian cancer was identified. Patients received paclitaxel 175-180 mg/m^2 and carboplatin at an AUC 5-6 over a maximum of six cycles. Fifteen participants received GJG at 7.5 g three times daily and 14 patients had no supportive treatment (Kaku *et al.* 2012).

The RCT of Kono 2013 had adequate allocation procedure, randomization and blinding. Blinding of outcome assessment was performed. The sample size was sufficient. Follow-up of one year was adequate. An intention-to-treat analysis was performed and narrow confidence intervals were shown (Kono *et al.* 2013).

The trial of Nishioka 2011 was not blinded and not placebo-controlled. It was claimed as randomized but exact procedure of randomization and allocation were not described. The study lacked from an insufficient sample size (Nishioka *et al.* 2011).

The trial of Kaku 2012 was small of size. Randomization procedures were not described. It was a multi-centre trial but no blinding of patients and personnel was performed (Kaku *et al.* 2012).

The trial of Kono 2013 was graded 1 B (CEBM) and 1+ (SIGN). Methodical limitations such as lack of blinding, no placebo control and insufficient sample size led to down- grading the trial of Nishioka 2011 to CEBM level 2B- and SIGN level 1- (Nishioka *et al.* 2011). The third trial was graded 2B- (CEBM)and 1-(SIGN) due to small sample size and un-blinded design (OCEBM Levels of Evidence Working Group 2011, Kaku *et al.* 2012, Scottish Intercollegiate Guidelines Network 2014).

Results

Primary outcome in the trial of Kono 2013 was CIPN until 8th course. Grade 2 or higher CIPN was detected in 17 of 44 (39%) in the GJG arm and in 23 of 45 (51%) in the placebo arm (RR 0.76; 95% CI 0.47 to 1.21). Grade 3 neuropathy was detected in three of 44 patients in the GJG group and in six of 44 patients in the placebo group (RR 0.51; 95% CI 0.14 to 1.92) (Kono *et al.* 2013).

Nishioka et al. 2011 assessed the incidence of CIPN grade 3 or higher as the primary outcome. After ten courses oxaliplatin-induced peripheral neuropathy was detected in none of the 22 patients receiving GJG and in three of 23 (12%) of the participants without treatment (RR 0.15; 95% CI 0.01 to 2.73).

After 20 courses grade ≥3 neurotoxicity was seen in seven of 22 patients (33%) in the GJG arm and in 17 of 23 (75%) in the control arm, respectively. Calculated Risk Ratio was 0.43 (95% CI 0.22 to 0.83) favoring the GJG arm. But no significant differences were found in grade 1-2 CIPN (Nishioka *et al.* 2011).

The results for grade 3 neuropathy could be pooled in meta-analysis. The overall- effect was RR 0.45; 95% CI 0.25 to 0.80 and thus significantly favoring GJG (see figure 14).

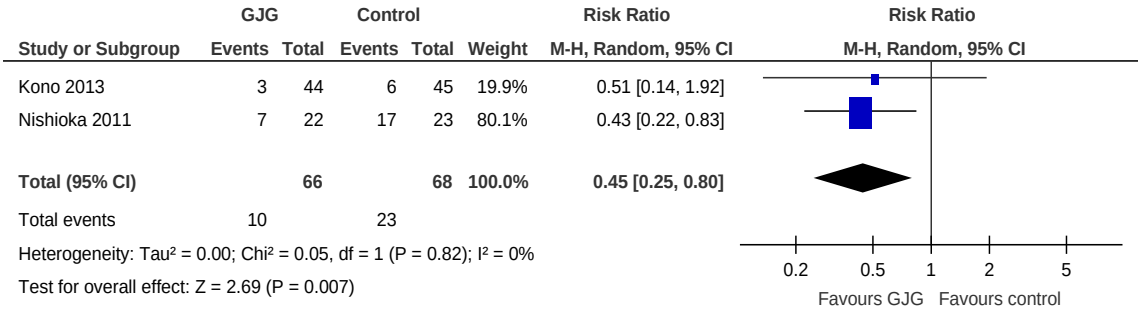

Figure 14: Forest plot for comparison of CIPN NCI-CTCAE (grade 3) GJG arm versus control

In the study of Kaku 2011 six of 15 patients in the GJG arm and five of 14 in the control arm experienced grade ≥2 CIPN caused by paclitaxel/carboplatin (RR 1.12; 95% CI 0.44 to 2.86). Neither scores for perception thresholds nor for neuropathy measured with VAS differed significantly between the study groups at any point of assessment (Kaku *et al.* 2012).

FACT-GOG-Ntx 12 did not differ significantly between study groups (Kono *et al.* 2013, Yoshida *et al.* 2013).

Tumor response rates were evaluated in two trials (Nishioka *et al.* 2011, Kono *et al.* 2013). No significant differences were detected. Partial response was seen in 14 of 27 patients (51%) and ten of 23 patients (43%) in the GJG and placebo arm, respectively (RR 1.19, 95% CI 0.66 to 2.15) (Kono *et al.* 2013).

In the trial of Nishioka 2011 15 of 22 (68%) of the GJG patients and 13 of 23 (57%) of the controls experienced a partial response (RR 1.21; 95% CI 0.76 to 1.91)(Nishioka *et al.* 2011).

Adverse events were similar in the intervention and control groups in both trials. No Goshajinkigan- related adverse events appeared (Kono *et al.* 2011, Nishioka *et al.* 2011). No secondary outcomes were reported in the trial of Kaku 2011 (Kaku *et al.* 2012).

Neurotropin

Characteristics and grading evidence

One Chinese study to investigate the effect of neurotropin in prevention of oxaliplatin-induced peripheral neuropathy was identified. It included 80 patients with colorectal cancer stage II and III, 38 evaluable for the intervention group and 41 for the control group. In this pilot trial patients were scheduled to receive XELOX regimen over eight cycles consisting of 130 mg/m^2 oxaliplatin on day one and capecitabine 1,000 mg/m^2 on day one to fourteen. Neurotropin was given at dosages of eight international units (IU) twice a day on day one to fourteen in the intervention group. The control group did not receive any treatment (Zhang *et al.* 2012).

The trial of Zhang 2011 was graded with 2B (CEBM) and 1- (SIGN) due to lack of blinding and small sample size (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

Neurotoxicity was assessed with NCI-CTCAE and OSS. All patients suffered from neurotoxicity grade 1. Patients in the intervention group had significantly less grade 2 or higher CIPN (RR 0.34; 95% CI 0.17 to 0.65). Though, the results for grade 3 or higher neurotoxicity did not differ significantly between groups (RR 0.11; 95% CI 0.01 to 2.05). Grade 1 neurotoxicity assessed with OSS was observed in all patients of both groups and grade≥2 neurotoxicity in five of 38 participants and 21 of 40 participants in the intervention and control group, respectively (RR 0.25; 95% CI 0.11 to 0.60). Again, no significant difference was found for grade ≥3 neurotoxicity (RR 0.12; 95% CI 0.01 to 2.15) (Zhang *et al.* 2012).

No significant differences in the appearance of other toxicities were observed between the study groups. Median number of chemotherapy cycles was 5.2 months in the control group. No further outcomes were reported (Zhang *et al.* 2012).

Nimodipine

One trial investigating nimodipine for cisplatin- induced neurotoxicity met eligibility criteria. Fifty-one patients with ovarian cancer took part in this RCT. They were scheduled to receive cisplatin 100 mg/m^2 and cyclophosphamide 750 mg/m^2 for six cycles. Twenty-four participants received nimodipine and 26 patients a placebo. The study drug was administered with a maximum daily dose of 360 mg, given up to four times a day (Cassidy *et al.* 1998).

The method of randomization and allocation was described and sufficient. The risk of bias was high due to inadequate observer and personnel blinding, small size and high drop-out rates. Thus, the trial was graded 2B-(CEBM) and 1-(SIGN) (Cassidy *et al.* 1998).

Results

The primary outcome was neurotoxicity assessed with a neurotoxicity score from 0 up to 17 points. This score summarized results from patient questionnaires and neurological examinations. High scores mean a higher intensity of CIPN. Forty patients provided data at 27 week endpoint. Neurotoxicity score was 10.4 ± 1.0 points in the intervention arm and 6.4 ± 0.8 in the placebo arm (MD 4.00; 95% CI 0.55 to 7.45). This significant difference between the study groups showed an unexpected reverse effect of nimodipine. Patients in the intervention arm suffered more likely from CIPN than participants taking placebo (Cassidy *et al.* 1998, OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Other adverse events were recorded with NCI-CTCAE criteria. Patients were planned to continue nimodipine after the finish of chemotherapy. Only 24 patients were available for analysis. Most patients dropped out due to nausea, vomiting and incompliance to the study drug. Though, no significant difference between the study groups was detected. According to the authors, no evidence for differences in OS was found, but exact data was not reported (Cassidy *et al.* 1998).

Omega-3 fatty acids (OFA)

Characteristics and grading evidence

One study investigated the efficacy of omega-3 fatty acids (OFA) for prevention of paclitaxel-induced peripheral neuropathy. Sixty-nine patients with breast cancer were randomized. Thirty participants in the intervention group received 640 mg OFA three times daily. In the control group, consisting of 27 patients, placebo was administered instead of the study drug. The patients were scheduled to receive 175 mg/m^2 of paclitaxel over four cycles (Ghoreishi *et al.* 2012).

The method of randomization and allocation concealment was adequate and described in detail. Blinding of participants and personnel was adequate, while there was no data for blinding of outcome assessment. Sample size of the trial was small and long- term follow-up was insufficient. Seventeen percent of the randomized patients were not evaluable for final analyses (Ghoreishi *et al.* 2012).

Therefore, the trial of Ghoreishi 2012 was graded with 2B (CEBM) 1- (SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

To evaluate neurotoxicity, the reduced Total Neuropathy Score (rTNS) and electro- physiologic studies were performed. The rTNS summarizes objective and subjective measures into a sum score with a maximum of 28 points. One to 10 points are considered as mild neuropathy, 11 to 19 as moderate and over 20 points as severe CIPN. In the OFA group nine of 30 patients (30%) did experience some grade of peripheral neurotoxicity. In the intervention group, six of 27 participants experienced CIPN (RR 1.35; 95% CI 0.55 to 3.30). No significant difference in severity of CIPN was found. The number needed to treat to prevent one patient from CIPN was three.

In addition, a significant difference in sural SNAP was detected. Whilst in the OFA group amplitude before treatment was 13.27 ± 5.02 μV and after treatment 13.33 ± 5.91 μV, in the placebo group sural SNAP decreased from 13.70 ±7 .46 μV to 9.74 ± 5.96 μV (MD 3.59 μv; 95% CI 0.50 to 6.68 μv). All other electro-physiologic measures showed no significant differences (Ghoreishi *et al.* 2012).

Oxcarbazepine

Characteristics and grading evidence

One trial investigating the potential beneficial effect of oxcarbazepine (OXC) in the prevention of oxaliplatin- induced CIPN was identified. This trial was included in the Cochrane review of Albers 2011. It included 40 patients with advanced colon cancer who were scheduled to receive 12 courses of oxaliplatin- based chemotherapy. Oxaliplatin was administered at dosages of 85 mg/m^2. The intervention group consisting of 20 participants received OXC starting with 150 mg/day on day one up to dosages of 600 mg/day. Patients in the control group received no treatment (Argyriou *et al.* 2006).

Method of allocation concealment and randomization was described in detail and was adequate. Patients allocated to the control group received no treatment. Personnel and outcome assessment were blinded. The sample size of the trial was small. An intention-to-treat analysis was performed (Argyriou *et al.* 2006). The study was graded 2B (CEBM) and 1- (SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

Clinical evaluation of neurotoxicity was based on the Neurologic Symptom Score (NSS) and the Neurologic Disability Score (NDS). In addition, electro-physiologic assessments were performed for the ulnar, median and superficial peroneal nerve unilaterally. All results were summarized in the modified Total Neuropathy Score (TNS). TNS graded CIPN as mild (1-11 points), moderate (12-23 points) and severe (>24 points). Neurotoxicity differed between study groups. In the OXC arm five of 16 (31%) patients reported CIPN compared to 12 of 16 (75%) in the control arm (RR 0.42; 95% CI 0.19 to 0.91). Not only the incidence but also severity of CIPN was higher in the control arm. Mean TNS scores were 4.1 ± 6.5 (range 0-17) in the OXC group and 11.2 ± 9.05 (range 0-28) in the control group (MD -7.10; 95% CI -12.56 to 1.64). In NDS a significant difference favoring the OXC arm was detected (MD -14.90; 95% CI -26.91 to-2.89). Scoring with NSS the MD was -0.90 (95% CI -1.67 to 0.13) (Argyriou *et al.* 2006, Albers *et al.* 2011).

Sixteen patients of each group completed the trial. Reasons for withdrawal were mainly disease progression and two drop-outs due to OXC- related events in the intervention group. Two patients reported dizziness and headache during administration of oxcarbazepine. Other adverse events were similar between the study groups. No data for survival rates were reported (Argyriou *et al.* 2006).

Recombinant Human Leukemia Inhibitory Factor (rhuLIF)

Characteristics and grading evidence

One trial investigating Recombinant Human Leukemia Inhibitory Factor (rhuLIF) for prevention of CIPN was identified. Patients included were treated with paclitaxel and carboplatin for the therapy of solid tumors. Paclitaxel at 175 mg/m^2 and carboplatin at an AUC of six were administered. A total of 117 patients were randomized into three groups. One group with 23 participants received rhuLIF at 2µg/kg. The second group with 26 patients was scheduled to receive rhuLIF at 4µg/kg and the third group with 30 patients received a placebo. The treatment plan was to start study treatment or placebo on day 1 of chemotherapy and continue rhuLIF/placebo up to day 6 (Davis *et al.* 2005).

The multicenter trial of Davis 2005 was described as randomized. Three groups existed, including one low-dose and one high-dose rhuLIF group and a placebo arm. The exact method of allocation was not described. Blinding of patients and personnel and objective assessment blinding seemed adequate. An intention-to-treat analysis was performed if patients had received at least one dose of the study drug. Only 33 of initially 117 randomized patients were

eligible for final analysis (Davis *et al.* 2005). The phase II- RCT of Davis 2005 was graded with 1B- (CEBM) and 1+ (SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014). The study's quality suffered from a high rate of drop-outs.

Results

The primary endpoint was the change in CIPN or symptoms of neuropathy from baseline to after four cycles of chemotherapy treatment. A CIPN score included measurement of nerve conduction velocities of the sural, median, ulnar and peroneal nerve. Scores ranged between zero to one. Additionally, H reflex-latencies, vibration perception threshold measures and quantitative assessments of CIPN symptoms were performed. In none of the assessments a significant difference could be found between the study groups. For example, patients with placebo had a 0.8 m/s better median nerve conduction than rhuLIF treated subjects (95% CI 2.7 to 1.2 m/s). Only changes of more than 1 m/s were considered relevant.

Quality of life was assessed with EORTC-QLQ 3 questionnaire. No significant differences between study groups were seen in terms of quality of life. Though, patients in the rhuLIF groups reported significantly greater improvement in global health status and less fatigue (no exact data given) (Davis *et al.* 2005).

Subcutaneous Bortezomib

Characteristics and grading evidence

One multi- center trial compared intravenous (i.v.) with subcutaneous (s.c.) protease inhibitor bortezomib. Precisely, s.c. bortezomib is no separate intervention than rather another form of application. Since it could be another chance of ameliorating CIPN, it should be considered in this review. Two hundred and twenty-two patients with relapsed multiple myeloma were randomized into the two study groups. Hundred forty-eight patients received s.c. bortezomib at the approved dosage of 1.3 mg/m^2. Intravenous bortezomib was administered at the same dosage to 74 participants. Patients received bortezomib up to eight cycles of 21 days and were allowed to have received one to three lines of previous treatment. Patients who had finished cycle four but had bad response rates could additionally receive oral dexamethasone 20 mg from fifth cycle onwards (Moreau *et al.* 2011).

The study was designed to compare safety of subcutaneous with intravenous bortezomib. The primary endpoint was overall response after four cycles of therapy instead of the incidence of CIPN. Method of randomization was described and adequate. Participants were randomized at

a 2:1 ratio. Authors described patient characteristics as “similar between groups with some exceptions” (Moreau *et al.* 2011). Details were not given. Patients and physicians were not blinded to allocation. An intention- to- treat analysis was performed. The sponsor of the study had full access to study data. The period of follow-up was adequate (Moreau *et al.* 2011). The study was graded with 1B- (CEBM) and 1+ (SIGN)(OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

CIPN was not a primary endpoint in this study. Peripheral neuropathy was assessed with NCI-CTCAE criteria. Incidence of CIPN of any grade was significantly lower when bortezomib was applied subcutaneously compared to intravenous injection (RR 0.66; 95% CI 0.58 to 0.76). Of note, 34 of 147 (23%) patients in the s.c. group and 21 of 74 (28%) patients in the i.v. group already suffered from grade 1 neurotoxicity at baseline evaluation.

In addition, time to onset of peripheral neuropathy was longer in the s.c. arm than in the i.v. arm. Cumulative dose at first onset of symptoms of CIPN was higher in the s.c. arm (41.0 mg/m^2; 95% CI 31.2 to not estimable) than in the i.v. arm (25.1 mg/m^2; 95% CI 18.2 to 39.4) (Moreau *et al.* 2011).

Overall response rates after four (42%) and eight cycles (52%) were similar between both groups. Non- inferiority of s.c. bortezomib in patient survival and response rates could be proven. Overall response rate difference was -0.4% (95% CI -14.3 to 13.5). Response improvement after additional dexamethasone when results after cycle 4 were suboptimal was 13 % in both groups. No significant differences in time to progression were found (s.c. group: 10.4 month; 95% CI 8.5 to 11.7. i.v. group: 9.4 month; 95% CI 7.6 to 10.6).

With borderline significance, rates of adverse events higher than grade 2 were more common in the i.v. group (52 of 74) than in the s.c. group (84 of 147) (RR 0.81; 95% CI 0.66 to 1.00).

Diarrhea was seen in 24% of the s.c. group patients and in 36% of the i.v. group (OR 0.65; 95% CI 0.43 to 0.99).

Thirty-one percent of the patients needed a dose reduction of s.c. bortezomib compared to 43% receiving i.v. study drug. In nine of 147 participants (6%) a local reaction to s.c. bortezomib was seen, such as redness, which led to a dose reduction in two patients. All cutaneous adverse events were resolved after a maximum of six days (Moreau *et al.* 2011).

Vitamin E

Characteristics and grading evidence

Our search identified five RCTs with a total of 426 participants fulfilling the selection criteria and to evaluate the protective effect of vitamin E against neurotoxic CTX. Two cisplatin trials were included in Albers 2011 (Pace *et al.* 2003, Argyriou *et al.* 2005).

An additional RCT for cisplatin- induced CIPN was identified (Pace *et al.* 2010).

One trial investigated the effects of vitamin E against oxaliplatin-induced neurotoxicity (Afonseca *et al.* 2013).

Kottschade 2011 with 207 participants evaluated the neuroprotective effect of vitamin E on patients treated with neurotoxic agents in general. In the following an overview of the included trials is given:

- Cisplatin for a variety of solid tumors (54 vitamin E treated patients and 54 control patients) (Pace *et al.* 2010).
- Cisplatin- based regimens for a variety of cancers (14 vitamin E treated patients and 16 control patients) (Argyriou *et al.* 2005).
- Cisplatin for a variety of solid tumors (13 vitamin E treated patients and 14 control patients) (Pace *et al.* 2003).
- Oxaliplatin- based regimes for colorectal and gastric cancer (18 vitamin E treated patients and 16 control patients) (Afonseca *et al.* 2013).
- Neurotoxic agents like oxaliplatin (26%), cisplatin, carboplatin, taxanes (58%) or combination (96 vitamin E treated patients and 93 control patients) (Kottschade *et al.* 2011).

Dosages of vitamin E varied from 300 up to 600 mg per day. In Pace 2003 and 2010 cisplatin was administered at dosages above 300 mg/m^2. In Argyriou 2005 cisplatin dosages varied dependent on the individual cancer. Other antineoplastic agents were combined with cisplatin, five patients additionally received docetaxel, another potential neurotoxic agent.

Oxaliplatin- based regimens were applied in one trial. Before application of vitamin E, calcium and magnesium supplements were administered in both the treatment and the control arm, respectively (Afonseca *et al.*2013). One study investigated the effect of vitamin E against neurotoxic agents in general. Oxaliplatin (26%), Cisplatin, Carboplatin, Taxanes (58%) or a combination of these were given (Kottschade *et al.* 2011).

Method of randomization was unclear in Pace 2003 and Argyriou 2006 (Albers 2011). In one trial randomization was performed by a dynamic allocation procedure that evened out

distributions of the stratification proceeded before (Kottschade *et al.* 2011). Pace 2010 and Afonseca 2013 used adequate methods for sequence generation and allocation concealment.

No subject and observer blinding was done in Pace 2003 and Argyriou 2006, control participants received no treatment.

In Afonseca 2013, Kottschade 2011 and Pace 2010 subjects received vitamin E or placebo. In these three studies observers were blinded as well.

In the study of Pace 2003 details provided on withdrawals, follow-ups and drop outs were insufficient.

In one study no ITT analysis was performed and a high number of drop outs due to disease progression may have influenced the results (Pace *et al.* 2010). In Kottschade 2013 additional to the application of vitamin E, calcium and magnesium infusions were used in both groups. Thus a possible interaction between both supportive therapies cannot be foreclosed. For details see figure 15.

The Cochrane review Albers 2011, including the trials of Pace 2003 and Argyriou 2006 (both graded 2B (CEBM) and 1- (SIGN) due to small sample size and lack of blinding was graded with 1A (CEBM) and 1++ (SIGN). Afonseca 2013 was graded 2B (CEBM) and 1- (SIGN) according to the very small number of participants. One study was graded 1B-(CEBM) and 1- (SIGN) due to a high rate of drop outs (Pace 2010). The study of Kottschade et al. received 1B (CEBM) and 1+ (SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

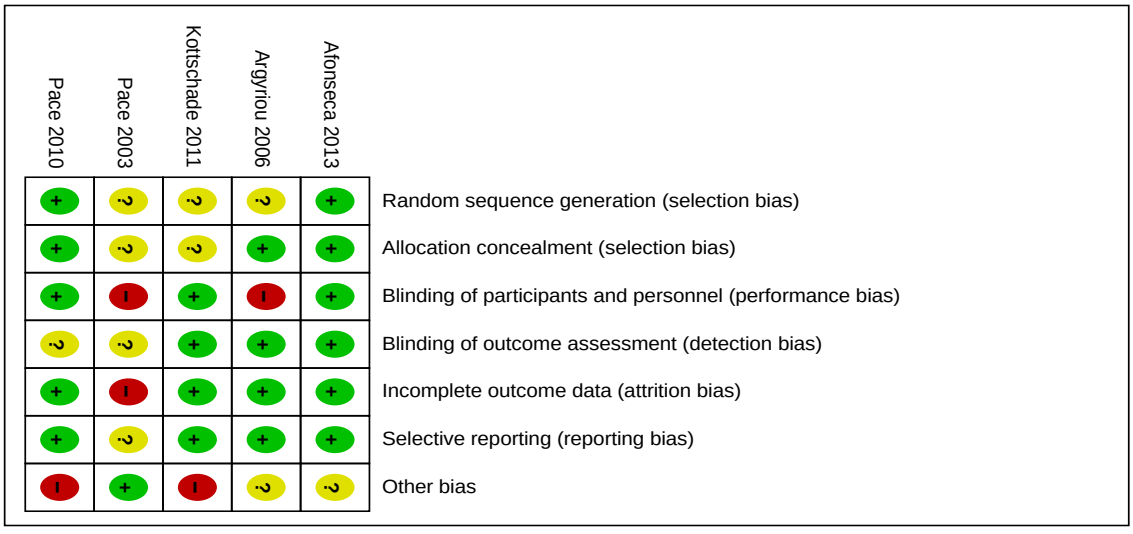

Figure 15: Vitamin E- Risk of bias summary
Note: + indicates criteria were met, ? indicates not reported, no detail, uncertain if the criteria were met, - indicates criteria were not met

Results

Afonseca 2013 and Kottschade 2011 used NCI-CTCAE as outcome measure for assessment of CIPN. Afonseca 2013 reported no significant differences in neurotoxicity between both groups (RR 1.21; 95% CI 0.82 to 1.79). The second study did not find differences in appearance of neurotoxicity, as well. Kottschade 2011 used higher dosages of vitamin E and could not state any significant difference between the groups (RR 0.97; 95% CI 0.54 to 1.74). The overall effect RR was 1.13 (95% CI 0.82 to 1.57) and thus no significant difference between the study groups could be shown.

Both Pace trials used the TNS for assessment of CIPN. Pooling the results of both studies, significantly less patients suffered from CIPN in the treatment arm (RR 0.41, 95% CI 0.23 to 0.73).

Pace 2003 discovered a greater number of patients developing CIPN higher than grade 3 in the control group compared to the vitamin E arm (RR 0.36; 95% CI 0.15 to 0.83).

In Pace 2010 one of 17 patients (5.9%) suffered from neurotoxicity grade >3 in the vitamin E arm compared to ten of 24 participants (41.7%) in the placebo arm (RR 0.46; 95% CI 0.21 to 1.00).

In figure 16 the pooled results for NCI-CTCAE and TNS scores are presented. In addition, incidence rates for all studies were pooled in a subgroup. The overall effect RR was 0.63 (95% CI 0.35 to 1.12) and thus showed no superiority of vitamin E.

A trend versus more diarrhea was observed in patients treated with vitamin E (55.6% vs. 18.8%) in Afonseca 2013. No further toxicities were reported.

No other secondary outcome measures were collected.

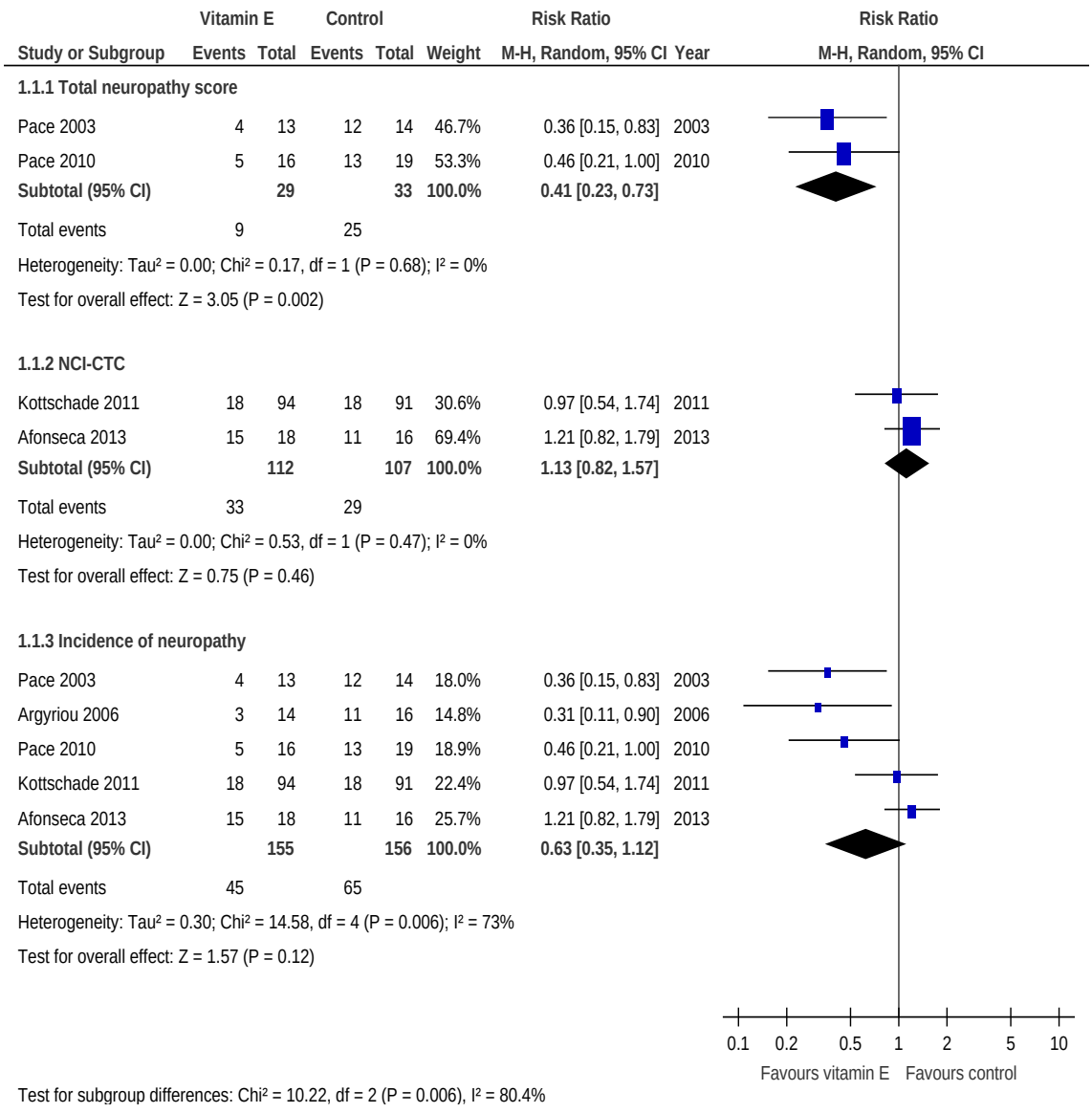

Figure 16: Forest plot for comparison of Vitamin E arm versus control. Subgroups of TNS, CIPN NCI-CTCAE and incidence of CIPN

3.4.2 Therapy of CIPN

Amitriptyline

Characteristics and grading evidence

Only a single RCT investigating the efficacy of amitriptyline in therapy of CIPN was performed. Patients who were eligible for inclusion needed to have a duration of chemotherapy for at least two month which lead to CIPN with an at least three point score on a scale from zero to ten. Twenty-two of a total of 44 patients received amitriptyline at 10 or 25 mg. The dosage was increased up to 50 mg daily. Twenty-two patients were allocated to the placebo group (Kautio *et al.* 2008).

Random sequence allocation was generated by computer. Patients and personnel were blinded adequately. The sample size of the trial was rather small. The time to follow-up was adequate and an intention-to- treat analysis was performed (Kautio *et al.* 2008).

The study of Kautio 2008 was graded with 2B (CEBM) 1-(SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

Primary endpoint was the assessment of sensory and motor neuropathy with NCI-CTCAE. Additionally, patients filled in a diary of neuropathic symptoms using numeric scales. At the end of the study, global improvement of CIPN was graded with a five point numeric scale. A trend towards more improvement in the amitriptyline group was seen but with no statistical significance, according to the author's statement (Kautio 2008). Exact values were not reported. According to NCI-CTCAE criteria, no significant differences between groups in the severity of motor and sensory neuropathy were detected. Here, as well, no numbers were given in the study protocol (Kautio *et al.* 2008).

The assessment of QoL was a secondary endpoint. It was measured by EORTC-QLQ- C30 questionnaire. A positive effect of amitriptyline was observed ($p=0.038$). The other categories showed no significant differences.

Only 33 of the 44 patients were eligible for final analysis. Three withdrew from the study due to adverse events (all placebo group), four patients experienced cessation of neurotoxic chemotherapy during titration period (2 pat. in both arms) and two patients were not compliant (in each arm one patient) (Kautio *et al.* 2008).

Duloxetine

Characteristics and grading evidence

One trial investigating duloxetine in therapy of CIPN was identified. The large randomized, double blinded phase 3- study enrolled 231 patients with grade 1 or higher CIPN according to NCI- CTCAE criteria and 4 or more points on a scale from 0-10 counts for assessment of neuropathic pain. Patients were eligible if they had had CTX over at least three month against any kind of cancer. Participants were stratified by neurotoxic agent (paclitaxel, oxaliplatin, other taxanes or other platinum). The trial had a cross- over design. One hundred and fifteen patients were allocated to group A receiving up to 60 mg duloxetine daily in the first study period and then placebo in cross- over period. The procedure with the 116 patients of group B was similar but vice- versa (Smith *et al.* 2013).

The RCT had adequate randomization and allocation procedures. It was blinded to participants and personnel. Validated outcome measures were used and follow- up was adequate. Blinding of objective assessment was performed. The study had a cross- over design. After the initial five weeks, a wash- out period of two weeks was followed by a cross- over period from week 8 to 12. The sample-size was adequate, too (Smith *et al.* 2013).

This well- conducted trial was graded 1B (CEBM) and 1+ (SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

Patients reported pain and functional status weekly by filling out the Brief Pain Inventory Short form (BPI-SF). In this RCT average pain assessed with BPI-SF was the primary outcome measure. After the initial four treatment weeks, patients of the duloxetine- first group reported a higher decrease in pain (mean change in score: 1.06; 95% CI 0.72 to 1.40) than the placebo- first group (mean change: 0.34; 95% CI 0.01 to 0.66). Fifty-nine percent of arm A reported some decrease in average pain compared to 38% in arm B. Subgroup exploratory analysis suggested that patients who had experienced platinum- induced neuropathy had a greater benefit from duloxetine than those treated with taxanes- based regimens. After cross over, the treatment effect remained statistically significant. The change in mean pain score for group A (placebo second) was 0.41 (95% CI 0.06 to 0.89) and for group B (duloxetine second) 1.42 (95% CI 0.97 to 1.87). Additionally, CIPN was assessed with FACT/GOG- Ntx and NCI-CTCAE criteria. Results from FACT/GOG- Ntx assessment showed a greater decrease in pain interfering with daily function for the duloxetine- first group (arm A: 7.9; 95% CI 5.4 to 10.5 versus arm B: 3.5; 95% CI 1.1 to 5.9).

Secondary outcome measure was the appearance of other adverse events assessed with NCI-CTCAE criteria. In the initial treatment period, 16% of the participants treated with duloxetine first and 27% treated with placebo reported grade 2 non-hematologic adverse events. Grade 3 was observed in 7% of the arm A- patients and 3% treated with placebo. Drop-out rates due to adverse events differed between groups (arm A 11% vs. arm B 1%), even though AE rates were similar between the groups.

Quality of life was measured with FACT/GOG- Ntx score. The mean change in total score was 2.44 (95% CI 0.43 to 4.45) for patients treated with duloxetine first compared to 0.87 (95% CI 1.09 to 2.82) (Smith *et al.* 2013).

Gabapentin

Characteristics and grading evidence

One trial investigating gabapentin as therapeutic option for CIPN met eligibility criteria. The multicenter, double-blinded trial enrolled 115 participants who had average pain scores of 4 or higher on a numeric rating scale (NRS) or one more count on the ECOG neuropathy scale (ENS). Patients were eligible when they had suffered from CIPN for at least one month. They could either still receive chemotherapy or have already finished it. Fifty-seven participants with any kind of cancer were allocated to the gabapentin- first group and received gabapentin at 300 mg capsules over six weeks (arm A). Over a period of three weeks a dose of nine capsules a day should be reached. Fifty-eight participants received placebo first (arm B). A two week wash-out was followed by a six week cross- over period (Rao *et al.* 2007).

Method of randomization and allocation procedure was described adequately. Patients and personnel were blinded. Blinding of outcome assessment was not described. The size of the study and follow-up were sufficient.

The trial of Rao 2007 had low risk of bias and was graded with 1B (CEBM) and 1+ (SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

The primary endpoint was pain measured with Numeric Rating Scale (NRS) or ECOG-Neuropathy scale (ENS). An improvement of CIPN measured with NRS was seen in all patients, no matter which group they belonged to (3.2 vs. 4.2, p=0.05). NRS improved by 0.12 units from baseline to study end (p= 0.03). Furthermore, CIPN was assessed with WHO scale and with the short form of McGill Pain Questionnaire, the Brief Pain Inventory Short Form, and the

Symptom Distress Scale. No statistically significant differences were detected in any of these endpoints (Rao *et al.* 2007). Only scores but no standard deviations were given.

As a secondary outcome quality of life was assessed with a QoL- scale. Adverse events were recorded weekly by using WHO-scale. Adverse events were seen equally in both groups. Twenty percent of the gabapentin group and 29% of the placebo arm stopped therapy early. Reasons were given as "refusal" and disease progression. No significant differences between groups were found (Rao *et al.* 2007). Just scores but no standard deviations were given.

Lamotrigine

Characteristics and grading evidence

One trial investigated the efficacy of Lamotrigine in manifested CIPN. Eligible for inclusion were patients with any kind of cancer who suffered from CIPN existing over at least one month induced by platinum compounds, taxanes or vinca alkaloids. One hundred thirty-one participants who had average pain scores of 4 or higher on a numeric rating scale (NRS) or one more count on the ECOG neuropathy scale (ENS) were included. Chemotherapeutic treatment could be ongoing or already finished. Lamotrigine was administered in 63 patients and placebo in 62 patients. Six patients were excluded before treatment was started. Initially, participants received 25 mg lamotrigine. Dosage was increased up to 300 mg daily (Rao *et al.* 2008).

The study was described as randomized but method of allocation and randomization were not presented. Patients and personnel were blinded to the study drug. Sample size and follow-up were adequate. Only 56 % of the patients in the lamotrigine group and 74 % of the placebo group were eligible for final analysis at the end of therapy after ten weeks (Rao *et al.* 2008).

The RCT of Rao 2008 was graded with level 2B (CEBM) and 1- (SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

Primary endpoint was pain measured with NRS or ENS. At the end of treatment, after ten weeks only 34 of 63 (56%) participants in the lamotrigine group and 46 of 62 (74%) patients in the placebo arm were eligible for analysis. No significant difference in change of neuropathic pain and symptoms was detected between the study groups. The NRS average score had decreased by 0.3 and 0.5 units in the intervention and control arm, respectively (p=0.56). No exact standard deviations were reported.

In addition, CIPN was assessed with WHO scale, with the short form of McGill Pain Questionnaire, the Brief Pain Inventory Short Form, and the Symptom Distress Scale.
Only slight differences were found in these assessments. Authors state that these differences could be explained by multiple testing but were not significant (Rao *et al.* 2008).

As a secondary outcome quality of life was assessed with a QoL- uniscale (single item of global QoL scale, numeric from 0 to 100). No exact data were reported. Adverse events were recorded weekly by using WHO-scale. No significant differences regarding quality of life or adverse events were detected between groups. Thus, patients of the lamotrigine group decided to leave the trial more often due to adverse events or patient refusal (33% vs. 18%; p=0.06) (Rao *et al.* 2008). We could not estimate RR due to not published exact data.

Nortriptyline

Characteristics and grading evidence

The efficacy of nortriptyline for therapy of cisplatin- induced neuropathy was investigated in one trial. Included were patients who had experienced treatment with cisplatin-based chemotherapy and who had at least one month of painful neuropathy. Fifty-one eligible patients were randomized in a cross-over design to either receive nortriptyline or placebo first. In the nortriptyline- first group 26 participants were scheduled to receive the study drug up to 100 mg. Twenty-five patients received placebo. The first period of 4 weeks was followed by cross-over period of the same duration. A wash-out period of one week was performed (Hammack *et al.* 2002).

The method of randomization and allocation was described adequately. The study was double-blinded and had a cross-over design. Wash-out period had duration of one week only. An intention-to-treat analysis was performed. The sample size was rather small. Outcome measures were validated but could not differentiate paresthesia from neuropathic pain (Hammack *et al.*2002).

The trial was graded 2B (CEBM) and 1- (SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

Authors claim a mild but uncertain beneficial effect of nortriptyline in treating CIPN induced by cisplatin. Change in pain and paresthesia was measured on a Visual Analogue Scale (VAS) from baseline. Paresthesia was reduced by 5% in the intervention first- arm compared to placebo first- arm. Of note, results for VAS measuring paresthesia were insignificant before and after

cross-over (p=0.78). Overall, 15 of 51 patients receiving the study drug reported ten points less pain, whilst only ten of 51 placebo patients did. Authors presumed a possible carry-over effect because results of the study periods were partly disparate.

In addition, the primary effect measure was unable to separate pain from paresthesia (Hammack *et al.* 2002). The risk ratio could not be calculated due to missing data.

Important to acknowledge is the higher rate of adverse events next to CIPN during the intervention phase. Participants in the nortriptyline arm had more dizziness (49% vs. 15%; p=0.002), more constipation (41% vs. 22%; p=0.07) and dry mouth (62% vs. 31%; p=0.002).

Topical Gel: Baclofen, Amitriptyline HCl, Ketamine (BAK)

Characteristics and grading evidence

One trial searched for the efficacy of a topical gel, consisting of baclofen, amitriptyline HCl and ketamine for therapy of CIPN. Patients who had received or who were under current CTX with symptoms of CIPN for at least one month were included. They were eligible if peripheral neuropathy had at least a four point score on a scale from zero to ten and was limited to hand or feet for application of the gel. The multicenter RCT included 208 patients, 101 in the BAK gel arm and 102 in the placebo group. The gel consisted of 10 mg baclofen, 40 mg amitriptyline HCl and 20 mg ketamine. The gel was applied to the locus of numbness, paresthesia, pain or tingling twice daily for over four weeks (Barton *et al.* 2011).

The method of randomization and allocation was deemed secure. The trial was described as randomized but the exact method was not reported. Additionally, the method of blinding was not described. Sample-size and follow-up were adequate. An ITT analysis was performed (Barton *et al.* 2010).

The study of Barton 2010 was graded with 1B- (CEBM) and 1+ (SIGN) (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

Results

Primary endpoint was the change in sensory neuropathy assessed with the EORTC-QLQ-CIPN 20 instrument. The scale includes nine items for different symptoms of neuropathy. The EORTC-CIPN 20 showed a modest trend favoring the BAK gel (mean: 8.1 ± 15.05) compared to placebo (mean: 3.8 ± 15.52). The calculated mean difference and its confidence interval was 4.30; 95% CI -0.59 to 9.19. Motor neuropathy showed corresponding results: BAK arm 7.1 ± 13.72 and for the placebo arm 1.8 ± 14.05 (MD 5.30; 95% CI 0.86 to 9.74).

Positive effects of BAK gel could also be observed looking at the individual items of the EORTC-CIPN 20 such as tingling, shoot or burning. The effects of the gel seemed to be more impressive in the upper extremities (Barton *et al.* 2010).

In addition, CIPN was measured with NCI-CTCAE criteria and single numeric analogue questions were answered by patients concerning the presence of tingling, numbness and pain. NCI-CTCAE values failed to show a certain positive effect. The single item questions mean changed from baseline 11.2 ± 20.53 and 6.3 ± 23.60 in the BAK arm and in the placebo arm, respectively (MD 4.90; 95% CI -2.18 to 11.98).

Secondary endpoints were scores in the BPI, in Profile of Mood States (POMS) and adverse effects. BPI and POMS scores did not differ significantly between the study arms. (no exact data given).

A high rate of drop-outs was observed. Twenty-six patients in the intervention and 27 patients in the placebo arm were not eligible for final analysis. Eleven patients withdrew due to adverse events in the BAK arm and eight in the placebo arm. However, no significant difference in the appearance of adverse events assessed with NCI-CTCAE could be found (Barton *et al.* 2010).

Venlafaxine

Characteristics and grading evidence

One trial investigated the efficacy of venlafaxine in patients with acute oxaliplatin-induced neuropathy during ongoing CTX. Patients were eligible if they were receiving oxaliplatin treatment every two weeks and reported an acute neuropathy. Neurotoxicity was evaluated with a 12-question Neuropathic Pain Symptom Inventory (NSPI) form during and after treatment. Forty-eight patients were scheduled to receive either venlafaxine hydrochloride at 50 mg prior to oxaliplatin and venlafaxine extended release from day 2 to day 11 at 37.5 mg or analogue placebo. Each group consisted of 24 patients. The dosage of oxaliplatin was not specified (Durand *et al.* 2012).

Allocation procedure and randomization were described adequately. Blinding of participants and personnel was performed. The sample size was insufficient. There was no data whether an ITT- analysis was performed.

The RCT of Durand 2011 was graded with CEBM level 2B- and SIGN level 1-.

Results

Primary endpoint was pain intensity and full pain relief under treatment assessed with NPSI, NRS and OSS. Functional impairment was assessed with a NRS from 0 to 100%. Six of 20

patients (31.3%) in the venlafaxine arm experienced full pain relief compared to one of 22 patients (5.3%) in the placebo arm (p=0.03). The calculated RR was RR 6.60 (95% CI 0.87 to 50.18).

Additionally, more patients in the intervention arm experienced a ≥ 50% relief of pain (venlafaxine arm: 14 of 20 patients (68.8%) vs. placebo: 6 of 22 (26.3%); RR 2.57; 95% CI 1.22 to 5.38).

Venlafaxine also reduced impairment of CIPN on functional status of the patients (p<0.0001). But no exact data was given.

Three month after the end of treatment, chronic CIPN was assessed. None of the participants was still under oxaliplatin chemotherapy. It was detected that more patients in the intervention arm showed grade 0 CIPN (8 of 20 pat; 38.5%) than in the placebo arm (1 of 22; 5.6%) (p=0.06). The calculated RR was 9.60 (95% CI 1.31 to 70.40) (Durand *et al.* 2011).

As secondary endpoints, adverse events were collected every two weeks and at the end of the study. Grade 1-2 nausea (RR 1.57; 95% CI 1.10 to 2.25), somnolence/asthenia (RR 2.50; 95% CI 1.38 to 4.53) and vomiting (RR 5.00; 95% CI 1.22 to 20.46) were seen significantly more often in the intervention group than in the control group. No grade 3 or 4 toxicities appeared in the venlafaxine arm (Durand *et al.* 2011).

4 Discussion

In this SR the efficacy of RCTs investigating medicinal prevention and therapy of CIPN is presented, graded and summarized. This dissertation was established as a part of the S3-guideline for "Supportive Care in Cancer Patients". The following recommendations were resolved in the S3-consensus conference.

This review included RCTs only and was based on a systematic literature search.

4.1 Discussion of methods

In general, our search strategy, method of data extraction, grading and calculation of effects were orientated on valid and common methods generating SRs and meta-analyses. All steps designing a SR and meta-analyses were according to the Cochrane Handbook (Higgins and Green 2011) and calculations performed with the program Review Manager 5.3.

For creating the search strategy we used the PICO scheme (Schardt *et al.* 2007). For processing the search strategy and reporting the performance of this meta-analysis we applied the PRISMA statement (Moher *et al*. 2009).

The search was conducted in three data bases. All RCTs having a comparable intervention and control group were pooled. Seeking studies in different sources minimized the chance of publication bias. Often though, studies with negative results or insignificant differences are not published (Higgins and Green 2011). Most trials show modest treatment effects. Other existing studies with negative results might not have been published. In addition, only German and English literature was searched and references in other languages were not considered. Starting with only screening by title or abstract, a final statement of reference's quality could not be made. Funnel plots, displaying publication bias, could not be created, since only few studies for one anti- neurotoxic agent could be found. Thus, the size of publication bias is difficult to estimate and it cannot be ruled out that publication bias exists in this review.

We also did not include or look for ongoing studies or unpublished studies. SRs published after creation of the tables of evidence were considered for discussion but not for the review as the new SR of Albers and the ASCO guideline (Albers *et al.* 2014, Hershman *et al.* 2014).

Search performed by three independent authors minimized selection bias. None of the searchers stated a conflict of interest.

Grading of the RCTs and SRs was performed according to SIGN and CEBM levels (OCEBM Levels of Evidence Working Group 2011, Scottish Intercollegiate Guidelines Network 2014).

For performing meta-analysis, we needed to decide which data could be pooled depending on clinical and statistical heterogeneity (Higgins *et al.* 2003, Higgins and Green 2011).

Even though the CIPN NCI-CTCAE criteria have limitations such as under-estimating CIPN and unambiguous grades, they were often used throughout the RCTs (Postma and Heimans 2000, Cavaletti *et al.* 2013). Different assessment methods, different times of assessment and the variety of study protocols and settings made it hard to conduct meta-analysis with low heterogeneity and bias. An overview to show the diversity of assessment methods is given in table 8.

Some of the calculations contain substantial statistical heterogeneity and thus were not pooled. When calculating overall effects, often a substantial heterogeneity was present.

In addition, frequently not all treatment effects of the named assessments were presented in the studies. Here again, selective reporting bias should be taken into account.

The process from the extracted and graded data to forming a recommendation and estimating its strength and the level of evidence was characterized by GRADE criteria (Grading of Recommendations Assessment, Development and Evaluation).

The results of this dissertation thesis have been discussed and consented in the working group "CIPN" of the S3 guideline and have been presented in the final consensus meeting for revision and reconciliation. Eligible for vote were all elected representatives. Methodical moderation was done by Dr. med. Markus Follmann (guideline program DKG) and Dr. med. Nothacker (AWMF).

Table 8: Outcome measures used throughout the studies and their comparability using the example of cisplatin

1. Cisplatin					
Reference	Patient assessments	Questionnaires	Clinical Functional Tests/ Scores	Semi quantitative/ Quantitative Measures	Meta-analysis possible?
ACTH-Analogue: Org 2766					
Roberts 1997				VPT	yes
Van Gerven 1994				VPT	yes
Hovestadt 1992				VPT	no
Van-der-Hoop 1990				VPT	yes
Alpha lipoic acid					
Guo 2013	NCI-CTCAE FACT-GOG-Ntx	BPI	Timed functional test		no
Amifostine					
Rick 2001	NCI-CTCAE				no
Planting 1999	NCI-CTCAE			VPT	no
Kemp 1996	NCI-CTCAE				yes
Diethyldithiocarbamate (DDTC)					
Gandara 1995	NCI-CTCAE				
Glutathione (GSH)					
Schmidinger 2000	WHO				no
Smyth 1997	NCI-CTCAE	HADS QoL Rotterdam			yes
Bogliun 1996			NDS NSS	VPT SNAPs	no
Cascinu 1995	WHO			SNAPs	no
Colombo 1995				SNAPs	yes
Magnesium sulfate and Magnesium sub carbonate					
Bodnar 2008	NCI-CTCAE				no
Nimodipine					
Cassidy 1995	NCI-CTCAE WHO		Neurotoxicity Score		no
Vitamine E					
Pace 2010			TNS	SNAP	yes
Argyriou 2006			Neurological Examination PNP-Score	SNAP	no
Pace 2003			TNS	SNAP	yes

4.2 Discussion of results

For the medicinal prevention and therapy of CIPN numerous studies exist. Many research teams investigated a broad variety of substances. For the issue of CIPN, some anti- neurotoxic agents are well-investigated, others are not.

A main problem of exploring CIPN is its assessment. Throughout the included trials various assessment methods could be found. It makes it hard to pool and compare results. In addition, some assessments underestimate, others overestimate CIPN, which makes it even harder to rate and review the subjective symptoms of chemotherapy- induced neurotoxicity.

Our search was performed up to June 2014. The ASCO guidelines of 2014 and the new Albers review of 2014 (Albers *et al.* 2014, Hershman *et al.* 2014) thus could not be considered for inclusion in the tables of evidence or the meta- analyses but will be taken into account for the discussion.

In the following results of the trials and meta-analyses and the resulting guidelines recommendations will be discussed.

4.2.1 Medicinal prevention of chemotherapy- induced peripheral neuropathy

For the prevention of CIPN we identified 58 randomized trials and three SRs. For some substances several well-conducted RCTs with high precision exist, for others only one, sometimes low-quality or small-sampled trial with resulting low precision could be found. Currently, none of the substances can be recommended for the prevention of CIPN.

The optimal supportive care substance must be secure, should have no or only mild side effects, should be affordable since CIPN has very high incidences and it must have no interference with the antineoplastic efficacy of the chemotherapy. In addition, it should be easy to use, so compliance in patients would be high.

Acetylcysteine was investigated in only a single trial. The study drug was known as a secure, affordable and convenient. Its mechanism of action is supposed to increase blood levels of glutathione and thus reduce the level of oxalate known as a possible cause for oxaliplatin-induced neuropathy (Cascinu *et al.* 2002, Lin *et al.* 2006). Authors of the trial of Lin 2006 described no decrease in electro-physiologic measures in the intervention group and a significant difference in the appearance of neurotoxicity between study arms. These results were ascribed to the impact of acetylcysteine by the authors (Lin *et al.* 2006).

Due to methodical restrictions, selective reporting and very small sample size this conclusion cannot be drawn. Lin 2006 is the only trial investigating the effect of acetylcysteine (Lin *et al.* 2006). Thus, no synthesis and comparison of study data was possible. No recommendation for the use of acetylcysteine was given in the S3- consensus conference. This conclusion is identical with the ASCO guidelines of 2014 and the review Albers 2014 (Albers *et al.* 2011, Hershman *et al.* 2014)

The usage of **acetyl-L-carnitine (ALC)** was researched in the large and well- conducted trial of Hershman 2013 (Hershman *et al.* 2013). ALC as a natural compound secures levels of acetyl-co- enzyme A which is responsible for the disposal of toxic metabolic products (Bieber 1988). It also plays a role for acetylation of tubulin which is responsible for neural protection. Animal trials showed a beneficial effect of ALC in neuro-protection (Pisano *et al.* 2003).
However, authors could not find that acetyl-L-carnitine was effective in preventing taxane-induced peripheral neurotoxicity. Results even showed that in the ALC group at 24-week follow-up CIPN was higher and functional status had decreased compared to the placebo arm. (Hershman *et al.* 2013). According to these results, the administration of ALC cannot be recommended for preventing CIPN and new trials fail to be promising. This recommendation goes along with the ASCO guidelines of 2014 (Hershman *et al.* 2014).

In cultural tissue studies, **ACTH- Analogue: Org 2766** led to neurite growth (Strand 2000) and was known to ameliorate or even prevent CIPN (van der Hoop *et al.* 1990, Muller *et al.* 1992, Koeppen *et al.* 2004).
Results of the included studies exploring the efficacy of the ACTH- Analogue Org 2766 are heterogeneous. While the later vincristine trial did not find a beneficial effect of Org 2766 preventing CIPN, the earlier trial reported a possible benefit using the ACTH- analogue in prevention of vincristine induced peripheral neuropathy (van Kooten *et al.* 1992, Koeppen *et al.* 2004). Van Kooten 1992 sees limitations of the study in the small sample size and significant differences in mean age between the study groups. Patients in the placebo group had a mean age of 54.7 years compared to the intervention group with 44.7 years. Authors state that especially the older patients in the placebo group reported the most severe symptoms and thus no definite conclusion could be drawn (Van Kooten *et al.* 1992). The largest cisplatin trial with adequate blinding and statistical analysis negated a benefit from Org 2766 (Albers *et al.* 2011; Roberts *et al.* 1997). The trial of Van Gerven 1994 used different statistical analysis which had led to distinct results and thus no definite conclusion could be drawn either (Albers *et al.* 2011, Van Gerven *et al.* 1994). Authors of the second cisplatin trial found a possible benefit of the study drug but confessed that the study was extremely under-powered and had

a high drop-out rate (Hovestadt *et al.* 1992). The first trial found positive effects of Org 2766 in prevention of CIPN. But the study had inadequate statistical analysis and was small sized (Van-der-Hoop *et al.* 1990). The overall effect was not significant. For conclusion, a recommendation for the usage of the ACTH-analogue Org 2766 cannot be given. Additionally, Org 2766 is not available in the German-speaking world. Our recommendation was in accordance with ASCO 2014 and Albers 2014 (Albers *et al.* 2014, Hershman *et al.* 2014).

Alpha-lipoic acid as an antioxidant was explored in trials being effective against diabetic peripheral neuropathy (Ibrahimpasic 2013, Guo *et al.* 2014, Snedecor *et al.* 2014). It is supposed to be effective catching radicals of oxidation of platinum drugs in the dorsal root ganglia (Roelofs *et al.* 1984, Borcea *et al.* 1999, Evans and Halliwell 1999).
Authors of Guo 2013 found that with this trial the effect of alpha-lipoic acid could not be estimated. A high number of drop-outs limited the validity. Incompliance was explained with high dosages, high frequency and large size of alpha-lipoic acid. In this trial study medication was not administered two days before and four days after chemotherapy in concerns of interference with the antitumor efficacy. Authors referred to an earlier trial investigating alpha-lipoic acid's efficacy (Guo *et al.*2013). We did not include this study because no full study protocol was available (Gedlicka *et al.* 2002). Thus the trial of Guo 2013 was the only included, no data synthesis was possible. ALA cannot be recommended for preventing CIPN.
For the investigation of alpha-lipoic acid other well- designed RCTs are needed.
The same conclusion was drawn in the ASCO guidelines (Hershman *et al.* 2014).

Amifostine as a potential neuroprotective agent was researched in an animal model. Results showed an increase of neurite length and neurite-forming-cells (Ceresa *et al.* 2014).
Studies included in this SR were inconclusive in showing amifostine's anti-neurotoxic efficacy. Some even detected higher rates of side effects such as nausea, vomiting and hypotension (DeVos *et al.* 2005, Gelmon *et al.* 1999). The majority of the paclitaxel/carboplatin trials did not find a positive effect of amifostine in preventing CIPN. Two of the three cisplatin RCTs concluded that amifostine might help preventing CIPN (Planting *et al.* 1999, Kemp *et al.* 1996). One of the trials was not blinded. The overall effect of the performed meta-analysis was slightly favoring amifostine. Due to side effects caused by amifostine and in consensus with the ASCO guideline and the Cochrane review of Albers no recommendation for amifostine was given at the S3- consensus conference (Albers *et al.* 2014, Hershman *et al.* 2014).

Calcium and Magnesium infusions are probably the most discussed neuro-protective agent in the last decades. The interest on Ca/Mg infusions started with a retrospective and very

promising study of Gamelin 2004. Ninety-six patients received Ca/Mg before and after oxaliplatin-based regimen. Sixty-five patients were controls and received no neuro-protective agent. Results showed a withdrawal of only 4% of the patients in the Ca/Mg arm versus 31% in the control arm. Additionally, peripheral paresthesia and acute neuropathic symptoms were significantly lower in the intervention group, while tumor response rates were similar (Gamelin *et al.* 2004). According to these findings Ca/Mg infusions were applied in clinical practice to prevent from oxaliplatin- induced peripheral neuropathy and prospective trials were started (Pachman *et al.* 2015).

The CONcePT trial with 139 patients led to confusion. The study had a 2x2 design. The main aim was to compare continuous application of oxaliplatin-based regimens to intermittent application. Furthermore, patients receiving additional Ca/Mg infusion should be investigated. Due to slow recruitment randomization into the Ca/Mg arm was stopped early. After the trial was ongoing for two years it was terminated prematurely. The independent data monitoring committee had found a reduction of tumor response up to 52% in the Ca/Mg arm (Kurniali *et al.* 2010, Hochster *et al.* 2014). Due to these results, the French NEUROXA study of Gamelin 2008 published preliminary data showing no interference of Ca/Mg with antitumor efficacy of oxaliplatin and a positive effect in the prevention of CIPN (Gamelin *et al.* 2008). But up until today, no full publication was available. Alarmed by the results of the CONCepT trial, also other ongoing studies were closed prior to planned follow-up. Even though the studies lacked of power, in none of them a beneficial effect of Ca/Mg regarding CIPN could be detected (Chay *et al.* 2010, Ishibashi *et al.* 2010, Grothey *et al.* 2011).

Later on, the re-analysis of the CONCepT results did not find any harm of Ca/Mg regarding antitumor efficacy of oxaliplatin. Moreover, the CONcePT trial could not show an advantage of the Ca/Mg arm in terms of CIPN, either (Hochster *et al.* 2014). Of note, another double-blind, randomized trial of Dong 2010 was published in 2010. Since only the abstract was available, it was not included in our meta-analysis. The study of Dong et al. 2010 did also fail to show a beneficial effect of Ca/Mg in preventing CIPN (Dong *et al.* 2010).

The latest large and well- conducted prospective controlled trial did neither detect any benefit of Ca/Mg. In contrast to the preliminary results of the CONcePT trial no harm of the study drug could be detected (Loprinzi *et al.* 2014).

In order to summarize the results of the numerous studies, SRs were performed. The Chinese reviews of Wen 2013 and Wu 2012 included retrospective studies (Gamelin *et al.* 2004, Chaves *et al.* 2011, Knijn *et al.* 2011, Kono *et al.* 2011). All of the retrospective studies encouraged the use of Ca/Mg. Before knowing the results of ongoing prospective trials, Ca/Mg supplements

were induced into daily practice. The positive results of the respective trials also led to a rather positive statement for Ca/Mg in these SRs (Wu *et al.* 2012, Wen *et al.* 2013).

The latest Cochrane review led to the conclusion that results and pooled estimates of the included studies are "promising but inconclusive" (Albers *et al.* 2014).

Of note, the RCT of Loprinzi 2014 was not yet included in the Cochrane review of Albers 2014 due to time frame. Recently published ASCO guidelines made a recommendation moderately against Ca/Mg infusions (Hershman *et al.* 2014).

This recent meta-analysis fails to show a beneficial effect of Ca/Mg infusions for the prevention of oxaliplatin-induced peripheral neuropathy.

Two studies could be included to pool the effect of neurotoxicity of all grades assessed with NCI-CTCAE. Herein, no beneficial effect of Ca/Mg could be found (RR 0.95; 95% CI 0.69 to 1.32). Statistical heterogeneity was substantial with I^2=62%. The results of the studies were inconsistent. In the Ishibashi study only patients with a palliative setting were included, in Chay 2010 patients with palliative and curative setting participated (Chay *et al.* 2010, Ishibashi *et al.* 2010). The overall effect for neurotoxicity ≥ grade 2 was also indecisive comparing the study groups (RR 0.81, 95% 0.60 to 1.11).

For conclusion, our final meta-analysis fails to state a beneficial effect of Ca/Mg. But it does not interfere with the antitumor efficacy of oxaliplatin. The partly under-powered and prematurely terminated trials were hard to compare.

In accordance with the ASCO guideline and the review of Albers 2015 Calcium and Magnesium infusion cannot be recommended.

Carbamazepine is a Na (+) channel blocker. It was investigated to ease the neurotoxic effect of oxaliplatin in rats (Adelsberger *et al.* 2000).

The included trial of von Delius 2006 failed to find beneficial effects of carbamazepine in prevention of oxaliplatin- induced peripheral neuropathy (von Delius *et al.* 2007). An earlier study showed a beneficial effect of carbamazepine (Eckel *et al.* 2002). But since it was of very small sample size and randomized with a historical control group its significance is questionable (Von Delius *et al.* 2007). The observed side effects of carbamazepine should be investigated in further trials. Carbamazepine is a CYP 3A4 inhibitor and is likely to cause several interactions (Spina *et al.* 1996). Since all carbamazepine trials lacked of adequate sample size larger RCTs should be started to investigate possible benefits of carbamazepine. At the moment, no recommendation for carbamazepine can be given.

Diethyldithiocarbamate (DDTC) is a heavy- metal chelating agent. Animal and pharmacokinetic studies proved its safety and efficacy against cisplatin- induced neurotoxicity

(Gale *et al.* 1982, Evans *et al.* 1984). Earlier clinical trials were inconsistent (Rothenberg *et al.* 1988, Berry *et al.* 1990). Only the trial of Gandara 1995 investigating the effect of DDTC was found. This study only used one outcome measure for neurotoxicity. No significant differences were detected between the study groups. Furthermore, higher rates of toxicities such as nephrotoxicity, flushing, hyperglycemia, hypertension and withdrawals appeared in the DDTC arm. Authors concluded that DDTC is not preventing from CIPN. Since adverse events appeared in the intervention arm more often than in the control arm, DDTC was not investigated in later trials (Gandara *et al.* 1995). According to the ASCO guidelines and the review of Albers 2014, no recommendation for DDTC can be given (Albers *et al.* 2014, Hershman *et al.* 2014).

The authors of Loven 2009 described a clearly negative result for their pilot trial to show a beneficial effect of **glutamate** for prevention of paclitaxel and carboplatin- induced neuropathy (Loven *et al.* 2009).

Earlier trials investigated glutamine, being very similar to glutamate, which is supposed to stimulate nerve growth (Stubblefield *et al.* 2005). Additionally, glutamate was investigated to reduce cisplatin-, vincristine- and paclitaxel- induced neuropathy (Jackson *et al.* 1988, Boyle *et al.* 1996, 1999).

The latest trial of Loven 2009 had inadequate sample size, missing information about statistically significant differences between the groups and a high rate of drop- outs. Authors stated that the high number of patients who were not eligible for final analyses was mainly due to compliance problems. They concluded that further studies with higher dosages of glutamate should be conducted (Loven *et al.* 2009).

As such glutamate cannot be recommended for the prevention of CIPN.

This recommendation goes along with the ASCO guidelines 2014 (Hershman *et al.* 2014).

Glutamine is an amino acid which plays an important role in tissue reparation and as a nitrogen transporter for the synthesis of purines and pyrimidines (Bartlett *et al.* 1995, Savarese *et al.* 2003). An earlier trial reported neuroprotective effects of glutamine in patients with breast cancer treated with paclitaxel (Vahdat *et al.* 2001).

Only one Chinese RCT of Wang 2007 was identified which investigated the effects of glutamine in preventing CIPN. The trial was not blinded nor placebo-controlled which are major methodical restrictions. Results indicated that glutamine might be a beneficial agent in neuro-protection. Though, results for the different grades of CIPN and after different periods were inconsistent. Furthermore, clinical outcome assessments showed results rather favoring the usage of glutamine, whereas electro-physiologic assessments did not (Wang *et al.* 2007).

No recommendation for the usage of glutamine in clinical practice was given. To strengthen evidence, larger well- conducted RCTs are needed.

Glutathione (GSH) as an antioxidative agent, is known to prevent from accumulation of platinum adducts in the dorsal root ganglia (Gregg *et al.* 1992, Holmes *et al.* 1998, Leal *et al.* 2014). Five studies investigated the efficacy of GSH in the prevention of cisplatin- induced peripheral neuropathy (Schmidinger *et al.* 2000, Smyth *et al.* 1997, Bogliun *et al.* 1996, Cascinu *et al.* 1995, Colombo *et al.* 1995). Considering NCI-CTCAE criteria for meta- analysis the overall effect was not significant and studies had substantial statistical heterogeneity. In addition the included trials lacked of methodical restrictions and sample size.

Two studies investigated the efficacy of GSH against oxaliplatin- induced neuropathy. Cascinu 2002 reported significant results favoring GSH (Milla *et al.* 2009, Cascinu *et al.* 2002).

In conclusion, a recommendation for using glutathione in prevention of CIPN in oxaliplatin or cisplatin- treated patients cannot be given at this time.

The only large trial investigating GSH in patients receiving paclitaxel/carboplatin regimens reported negative results (Leal *et al.* 2014). GSH should not be used in prevention of paclitaxel/carboplatin- induced CIPN.

This recommendation coincides with the ASCO guidelines (Hershman *et al.* 2014). In the review of Albers, the overall treatment effect is described as "hard to judge" (Albers *et al.* 2014).

Goshajinkigan is a traditional Japanese herbal medicine which has been used for treating diabetic neuropathy (Tawata *et al.* 1994, Nagaki *et al.* 2003, Uno *et al.* 2005).

Three trials investigated the Japanese herb Goshajinkigan for prevention of CIPN. Two trials were not blinded and no placebo- control was performed. Insufficient sample size and insignificant confidence intervals were major methodical restrictions.

Authors of Kono 2013 stated a beneficial effect of GJG, an abstract of this study was already published in 2009. The RCT was well-conducted with narrow-confidence intervals and low risk of bias. Though, patients were treated with Ca/Mg infusions as well. Ca/Mg infusions were prohibited during the 26 week treatment with GJG. But one cannot rule out the possibility of interactions between the study drugs. However, a trend towards a protective effect of GJG delaying CIPN of grade 2 and greater was found, the treatment effect was not significant (Kono *et al.* 2013).

In Nishioka 2011, GJG was also investigated in combination with oxaliplatin- based regimen in 45 patients and authors concluded that GJG is useful for preventing CIPN in patients with

oxaliplatin-based chemotherapy. Calculating the risk ratio for grade 3 or higher CIPN, a significant difference favoring the administration of GJG could be found (RR 0.45; 95% CI 0.25 to 0.80) (Nishioka *et al.* 2011). Pooling the effects of both studies, an overall effect significantly favoring GJG was calculated.

The paclitaxel/carboplatin trial of Kaku 2012 did not find any significant differences between study groups (Kaku *et al.* 2012).

In the trials of Kono 2013 and Nishioka 2011 no influence of GJG on antitumor efficacy was seen. Additionally no adverse events related to the study drug could be detected (Kono *et al.* 2013, Nishioka *et al.* 2011).

Goshajinkigan might be a new option for preventing oxaliplatin- induced peripheral neuropathy. But before a concrete recommendation can be given, further large and well-conducted trials must be performed to secure the quality of data. Furthermore, GJG is not available in the German- speaking world. No recommendation for using GJG in prevention of CIPN was given at the S3- consensus conference.

This recommendation coincides with the ASCO guidelines (Hershman *et al.* 2014).

Neurotropin was investigated in animal and human studies. It is used to treat peripheral neuropathies, chronic pain and post-herpetic neuralgia (Zhang *et al.* 2012). An animal study found out that neurotropin can prevent CIPN induced by oxaliplatin in rats (Kawashiri *et al.* 2011).

One Chinese pilot RCT of Zhang was identified which investigated the effects of neurotropin preventing oxaliplatin- induced peripheral neurotoxicity. Methodical limitations as the lack of blinding and placebo-control compromise the validity of the trial. Authors stated that neurotropin might be a promising beneficial agent in neuro-protection.

No recommendation for the usage of glutamine in clinical practice was given. To strengthen evidence, larger well- conducted RCTs are needed.

Nimodipine is a dihydropiridine calcium antagonist. It is used for prevention of cerebral vasospasm after sub-arachnoid hemorrhage. A rat model study showed neuro-protective effects against cisplatin- induced neurotoxicity (Hamers *et al.* 1991).

One randomized, placebo- controlled trial by Cassidy was initiated to investigate nimodipine for preventing CIPN. This trial brought not only negative results, it even concluded that the intervention group had higher rates of cisplatin-induced peripheral neurotoxicity. The number of drop-outs was inacceptable high. Authors decided against further patient accrual due to nausea, vomiting and bad patient compliance. These adverse events could not be surely related to the study drug. Since a reverse effect of nimodipine was detected and according to

the ASCO guidelines it can surely not be recommended for preventing CIPN (Cassidy *et al.* 1998, Hershman *et al.* 2014).

Omega-3 fatty acids (OFA) are polyunsaturated fatty acids. They appear in the phospholipid membrane of cells of the nervous system (Ghoreishi *et al.* 2012). They take part in neuro-regulation and signal transduction (Mazza *et al.* 2007).

The RCT of Ghoreishi 2012 was the first and only trial investigating omega-3 fatty acids for prevention of paclitaxel- induced peripheral neuropathy. Its findings support the usage of OFA as a neuro-protective agent. Major limitations to the study are its relatively small sample size and the lack of long term follow up. In addition, only in one of the neuro-physiologic measures a protective effect of OFA was detected. A lack of survival or tumor progression rates limit the statement OFA possibly effects antitumor efficacy of paclitaxel. Currently, omega-3 fatty acids cannot be recommended for clinical usage. Results of larger, well-conducted trials are needed (Ghoreishi *et al.* 2012).

Oxcarbazepine interferes with voltage-gated sodium channels. It is similar to the structure of carbamazepine, an antiepileptic drug. In addition OXC is supposed to effect calcium channels (Schmidt and Elger 2004, Argyriou *et al.* 2006).

Only one trial investigated OXC as potential preventive agent for CIPN in oxaliplatin-treated patients. The study was open-labeled, not placebo- controlled and of small size. Data ensuring that OXC does not interfere with oxaliplatin are missing. But results favored the use of OXC in prevention of CIPN. Electro-physiologic results showed beneficial effects for sural and superficial peroneal nerves but not for peroneal motor and ulnar nerves. Validated assessment score as the NDS and NSS as well supported a beneficial effect of OXC (Argyriou *et al.* 2006).

At the moment, no recommendation for the use of oxcarbazepine in clinical practice could be given. Further large and well- conducted RCTs are needed. This recommendation goes along with the Cochrane review of 2014 (Albers *et al.* 2014).

Recombinant Human Leukemia Inhibitory Factor (rhuLIF) is a modified cytokine. It was tested in phase I safety studies (Gunawardana *et al.* 2003). RhuLIF influences gene expression, proliferation and regeneration of neurons and monocytes (Davis *et al.* 2005). In vitro and animal models showed a beneficial effect of the cytokine in amelioration of CIPN (Curtis *et al.* 1994, Kurek *et al.* 1996, Group 2004).

Though, the RCT of Davis 2005 did not prove a beneficial effect of rhuLIF in prevention of CIPN in patients treated with paclitaxel and carboplatin. Authors claimed that the applied CPNE score was able to detect subclinical changes in nerve conduction velocity and that this was

corresponding with quality of life measuring instruments. However, no data were reported in the protocol.

The study has several limitations. It uses an assessment for CIPN which is not validated in other studies. Additionally, data for several items were missing: no confidence intervals were shown, p-values were missing, data for correlation of assessment with other scores, median age of groups and reasons for withdrawal were not reported in the study protocol.

Authors concluded that rhuLIF didn't seem very promising for the prevention of CIPN (Davis e*t al.* 2005). Thus, no recommendation can be given.

Vitamin E is an antioxidant. In animal trials, it has been researched for preventing from cisplatin- induced nephrotoxicity and ototoxicity (Kalkanis *et al.* 2004). Cisplatin is known to cause oxidative stress in cells and tissues (Weijl *et al.* 2004).

Five references were identified investigating the efficacy of vitamin E. The plain results of the Pace trials (Pace *et al.* 2010, Pace *et al.* 2003) and Argyriou 2006 encourage the use of vitamin E as a neuro-protective agent. But the quality of these RCTs is questionable. Two of the trials are not blinded and have a very small sample size (Pace *et al.* 2010, Pace *et al.* 2003, Argyriou *et al.* 2006). The later Pace trial included a higher number of patients (108 participants allocated) but only 41 of these could be considered in the analysis and no ITT analyses was performed. Afonseca 2013, another small sized trial, could not find statistically significant difference in favor of vitamin E (Afonseca *et al.* 2013). The latest bigger sized trial did not detect any significant differences between the study arms (Kottschade *et al.* 2011).

In conclusion, no recommendation for the use of vitamin E as a neuro-protective agent for the prevention of CIPN was given in the S3 consensus meeting. Large, high-quality RCTs are needed. This recommendation goes along with the ASCO guideline (Hershman *et al.* 2014) and the review of Albers 2014 (Albers *et al.* 2014).

4.2.2 Medicinal therapy of chemotherapy- induced peripheral neuropathy

For the therapy of CIPN we identified seven RCTs. New substances were researched as well as established medication used as antiepileptics, antidepressants or against neuropathic pain of other cause. Since therapeutic options are scarce, well known drugs should be considered to ameliorate CIPN even though the evidence for treating especially CIPN might be expandable.

Amitriptyline is a tricyclic antidepressant. It is well known to treat depressive disorders, mental disorder, bipolar disorder, post-herpetic neuralgia and neuropathic pain (Harding 1993, Saarto and Wiffen 2010, Dharmshaktu *et al.* 2012).

The RCT of Kautio 2008 failed to show significant positive effects of amitriptyline for treating chemotherapy-induced neurotoxicity. The only significant difference was observed regarding quality of life. Authors presume that the dose of amitriptyline was too low to show a benefit (Kautio *et al.* 2008). Additionally, the sample size of the study was insufficient. Larger, well-conducted RCT would be needed. As options of treating CIPN are rare, amitriptyline can be considered to milder CIPN. The ASCO guidelines support this recommendation (Hershman *et al.* 2014).

Another antidepressant, **Duloxetine**, a selective serotonin norepinephrine reuptake inhibitor, was researched in terms of treating CIPN. Serotonin and norepinephrine play an important role in inhibiting painful impulses to reach dorsal root ganglia (Willis and Westlund 1997). Duloxetine is known to be sufficient in the treatment of diabetic neuropathy (Goldstein *et al.* 2005, Wernicke *et al.* 2006).

The trial of Smith 2013 researched the SSRI for the treatment of CIPN. It was well- conducted, had a low risk of bias and an adequate sample size. Results support that duloxetine could be used for treatment of manifested CIPN with pain. Authors described that one limitation of their study was that the drop-out rate in the duloxetine- first arm was higher (11%) than in the placebo arm (1%). They conclude that this could be due to a higher number of patients experiencing grade 3 or higher AE in the duloxetine- first group. In addition, authors state that when enrolling patients in the RCT, they relied on NCI-CTCAE criteria which they described as "suboptimal" and with "poor sensitivity to detect subtle changes" (Smith *et al.* 2013).

Exploratory analyses showed that platinum- induced CIPN is affected more by duloxetine treatment than taxanes- induced neuropathy (Smith *et al.* 2013). Other studies to investigate this effect should be performed.

A significant difference between the duloxetine and the placebo group in the experience of neuropathic pain was detected. Therapy of CIPN with duloxetine should be considered. This recommendation given at the S3 consensus conference goes along with the ASCO guideline (Hershman *et al*.2014).

Gabapentin is used as antiepileptic and analgesic drug. It is used for mood disorders, seizures, pain syndromes, post herpetic and diabetic neuralgia. The structure of gabapentin is related to gamma-aminobutyric acid (GABA) which reduced neuron hyperexitability in an animal trial (Field *et al.* 1997, Luo *et al.* 2001).

The cross-over RCT of Rao 2007 failed to show beneficial effects of gabapentin used for therapy of CIPN (Rao *et al.* 2007). Since our options for treating CIPN are very rare, this well-

known drug can be considered for treatment of CIPN. The risk of side effects should be taken into account. This conclusion goes along with the ASCO guidelines (Hershman *et al*.2014).

Lamotrigine, also an anticonvulsant and drug against bipolar disorder, blocks sodium channels and thus reduces the distribution of neuro-transmitters. It has been researched to be effective against other pain syndromes (Vestergaard *et al.* 2001, Simpson *et al.* 2003, Zakrzewska and McMillan 2011).

The RCT of Rao 2008 reported that lamotrigine does not have therapeutic effects on CIPN. These results support a SR of Wiffer 2007 which stated that lamotrigine is ineffective for acute and chronic pain. Following these results lamotrigine should not be considered for the treatment of chemotherapy- induced peripheral neuropathy (Wiffen and Rees 2007, Rao *et al.* 2008).

The second generation tricyclic antidepressant **nortriptyline** is used for treating depression and nocturnal enuresis and sometimes for chronic pain. As amitriptyline it increases norepinephrine, serotonin and monoamines in the synaptic cleft (Sindrup *et al.* 2012).

Authors of the RCT of Hammack 2002 claim a mild but uncertain beneficial effect of nortriptyline in treating CIPN induced by cisplatin. They presumed a possible carry-over effect because results of the study periods were partly disparate. Results for VAS measuring paresthesia were insignificant before and significant after cross-over. This might be due to unblinding, a short wash-out, chance or to a psychological carry-over.

In addition, the primary effect measure was unable to separate pain from paresthesia (Hammack *et al.* 2002).

According to the results of this pilot study investigating the efficacy of nortriptyline in patients with cisplatin-induced peripheral neuropathy and the limited therapeutic options, the usage of this tricyclic antidepressant can be considered (Hammack *et al.* 2002).

Topical Gel: Baclofen, Amitriptyline HCl, Ketamine (BAK)

The results of the study of Barton 2010 showed a modest trend supporting the use of BAK gel in therapy of CIPN. Changes in EORTC-CIPN 20 scales for sensory and motor neuropathy were significant. Though, the effect size was not large. Authors presumed that the gel might have been under-dosed and that systemic efficacy might be very limited (Barton *et al.* 2010). According to these results a positive effect of BAK gel cannot be ensured, but a positive trend can be seen. Though, a final recommendation cannot be given. Since no harm was registered and the usage of the gel is easy to perform, patients should be informed about the gel and its side effects and costs (Hershman *et al*.2014).

4.3 Conclusion and outlook

For preventing chemotherapy- induced peripheral neurotoxicity so far no substance was identified to ensure a certain beneficial effect to ameliorate or protect from the signs and symptoms of CIPN. For being able to recommend one of the researched drugs, a substance with efficacy, few side effects and without interference with the chemotherapeutic drugs must be found.

A number of substances without substantial side effects were found. Acetylcysteine, Org 2766, alpha-lipoic acid, carbamazepine, glutamate, glutamine, glutathione, goshajinkigan, calcium/magnesium, neurotropin, omega-3 fatty acids, oxcarbazepine, rhuLIF and vitamin E did not cause severe toxicities other than CIPN but lacked of certain efficacy. Only amifostine, DDTC and nimodipine provoked inacceptable side effects.
In addition, numerous anti-neurotoxic agents were researched in a single study only, thus the evidence for a final recommendation was too low (acetylcysteine, alpha-lipoic acid, carbamazepine,DDTC, glutamate, glutamine, neurotropin, nimodipine, omega-3 fatty acids, oxcarbazepine, rhuLIF).
For amifostine, Org 2766, GSH, GJG, Ca/Mg and vitamin E more than one trial existed. But the results of the studies were inhomogeneous and conflicting, so no recommendation can be given. Not only the conflicting results, but also heterogeneity, lack of methodical quality and missing data interdict a final conclusion.
CIPN is a common side effect of chemotherapy which is largely compromising patient's daily living and quality of life. But due to lack of proven efficacy of the tested drugs, prevention still plays a very inferior role in clinical practice.
For the therapy of CIPN, the usage of duloxetine is recommended. In addition, minding the very limited options, also amitriptyline, gabapentin and nortriptyline can be considered for treatment of CIPN.

Of mention, following expert consensus, also opioids can be applied as therapeutic options are rare. Their side effects and the possible ceiling effect need to be taken into account (Alt-Epping *et al.* 2015). According to the literature available, no final recommendation can be given (Cartoni *et al.* 2012, Garassino *et al.* 2013). None of the existing studies investigating opioids and neuropathic pain was especially addressing CIPN and thus this issue was not included in this review.

Following the expert consensus also the topical use of capsaicin, lidocaine and menthol can be considered .

Furthermore, topical therapeutics are an option in ameliorating neuropathic pain. Baclofen gel showed positive effects compared to placebo in lowering the symptoms of CIPN. No toxic side effects appeared. Though, only one study exists further investigation is needed (Barton *et al.* 2011). In addition, Lidocaine and Capsaicin patches or a topical gel containing menthol can be applied (Kern *et al.* 2013, Maihöfner and Heskamp 2014, Alt-Epping *et al.* 2015, Fallon *et al.* 2015). The mentioned studies were not meeting our inclusion criteria as they were of retrospective nature or investigating not especially CIPN.

Researching CIPN and the preventive and therapeutic options has different issues.
Heterogeneous assessment methods make it hard to compare the studies and reliably survey the signs and symptoms of CIPN. Pooling data is hard to perform and often high statistical and clinical heterogeneity appears when comparing trials.
In addition, basic research concerning the pathogenesis of the various types of neuropathy and neurotoxicity is needed. Often, the mechanisms of action of the applied drugs are not entirely clear.
Furthermore, no randomized- controlled trials exist for other neurotoxic agents as thalidomide, lenalidomide or eribuline.
As the incidence of CIPN is high and it is limiting cancer therapy and quality o life in cancer patients, further well- conducted studies are urgently needed.

5 Summary

In this SR randomized controlled trials were searched and their study effects pooled in meta-analyses. All together 58 studies and three SRs were identified. In these RCTs 18 agents for the prevention and seven agents for the therapy of CIPN were investigated. None of the substances can be recommended for the prevention of CIPN. Some of these agents led to higher rates of side effects but mainly an adequate efficacy could not be proven for any of the agents.

Ca/Mg infusions were formerly widely discussed and even considered as harmful. Pooling the effects of only the fully published trials and including all recently published data, we could not detect a beneficial effect of Ca/Mg.

In treatment of CIPN, duloxetine and gabapentin are recommended. Furthermore, as therapeutic options are limited, amitriptyline and nortriptyline are suggested for the usage in clinical practice.

The main issue when comparing and pooling data is the inconsistency in the study populations, treatment regimens and effect measures which led to conflicting results.

Throughout the trials, different assessment methods were used and comparing data was difficult. For many substances only one trial existed. So even if it showed beneficial effects of the investigated drug, evidence is too weak to give a positive recommendation.

Next to the lack of methodical quality in many studies and to diverse assessment of CIPN, pathogenesis of CIPN and mechanisms of action of the study drugs must be investigated further. Chemotherapy- induced neurotoxicity is a common and burdening side effect of anti-cancer treatment and it even leads to interruption or dose reduction of chemotherapy. Thus, there is an urgent need for further investigation of path mechanisms, new and known agents and assessment of CIPN.

The results of this thesis are part of the S3- guideline of "Supportive Care in Cancer Patients". The results were consented by the elected representatives of the participating working groups and associations.

All recommendations were resolved at the S3-consensus conference.

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Theses

1. Antineoplastic agents often appear to be neurotoxic. Especially high incidences of chemotherapy- induced neurotoxicity (CIPN) result from treatment of cancer with platin derivates, taxanes, vinca alkaloids and bortezomib.
2. Currently, there is no standard assessment method for CIPN, which makes it difficult to compare the results of the studies. Often used are the NCI-CTCAE criteria for assessment of CIPN.
3. There is no evidence for the efficacy of any of the possible preventive drugs. At present, no effective medicinal prevention for CIPN exists.
4. Ca/Mg infusions are not effective in preventing CIPN (RR 0.81; 95% CI 0.58 to 1.14). Though, including all fully published RCTs, no harm concerning Ca/Mg interacting with the anti-tumor efficacy of oxaliplatin could be detected, either.
5. For the therapy of CIPN, duloxetine should be considered. A large Phase III-trial detected a statistically significant higher decrease in pain score in the intervention arm compared to the placebo arm (mean change in score: 1.06; 95% CI 0.72 to 1.40 vs. 0.34; 95% CI 0.01 to 0.66).
6. Due to limited options for treatment, the application of amitriptyline, gabapentin and venlafaxine can be considered. Possible side effects should be taken into account.
7. Further investigation of pathogenesis, assessment and other possible neuro-protective agents is urgently needed.
8. The results of this thesis are part of the evidence-based recommendations and statements of the S3- guideline " Supportive care in cancer patients" and were consented by the elected representatives of the participating organizations and working groups.

Appendices

Appendix 1- Search strategies

Pubmed Search on May 14th 2013

Structure	Search strategy	Hits
Taxanes	1 Taxoids	23069
	2 Paclitaxel	17742
	3 Docetaxel	6151
	4 Cabazitaxel	84
	1 OR 2 OR 3 OR 4	**23069**
Platinum compounds	5 Platinum compounds	38887
	6 Cisplatin	37855
	7 Oxaliplatin	3241
	8 Carboplatin	8386
	5 OR 6 OR 7 OR 8	**47602**
Bortezomib	**9 Bortezomib**	**2841**
Vinca alkaloids	10 Vinca alkaloids	31321
	11 Vincristine	3551
	12 Vinblastine	2144
	10 OR 11 OR 12	**31321**
Other chemotherapies	13 Lenalidomide	1015
	14 Thalidomide	5976
	15 Eribulin	80
	16 Epothilone	642
All CTX	**17 1-4 OR 5-8 OR 9 OR 13-16**	**93042**
CIPN	18 Peripheral Nervous System Diseases	118191
	19 Polyneuropathies	20546
	20 Nervous System diseases	1940996
	18 OR 19 OR 20	**1940996**
Chemotherapies AND CIPN	17 AND 18-20	7128
RCT only	**17 AND 18-20**	**265**
	21 Neuroprotective Agents	20080
	22 Protective Agents	133027
	23 Chemoprevention	11480
	24 Neoplasms	2426375
	25 Antineoplastic protocols	97464
Neuroprotective agents	26 Calcium	232809
	27 Magnesium	60032
	28 Carbamazepine	9172
	29 Gabapentine	2527
	30 Pregabaline	878
	31 Valproic Acid	9571
	32 Venlafaxine	1838
	33 Lamotrigine	2334
	34 Lidocaine	20803
	35 Fluoxetine	7154
	36 Duloxetine	946
	37 Topiramate	1976
	38 Amitriptyline	5845
	39 Menthol	1276

	40 Peppermint oil	158
	41 Capsaicin	8263
	42 Oxycodone	1162
	43 Adrenocorticotropic Hormone	44720
	44 Glutathione	43752
	45 Amifostine	1428
	46 Nerv Growth Factor	4971
	47 Neurotropin	1803
	48 Tocopherols	4898
	49 Acetyl carnitine	991
	50 21-23 OR 26-49	556952
Neuroprotective agents AND chemotherapies	51 50 AND 17	2689
Neuroprotective agents AND chemotherapies AND CIPN	52 51 AND 18-20	349
RCTs only	**52 RCT**	**50**
	53 Antineoplastic Agents AND Peripheral Nervous System Diseases	**193**
RCTs only		**175**
Summary	(17 AND 18-20) AND 52 AND 53	**490**

Medline Search on April 24th 2013

Structure	Search strategy	Hits
Design: RCTs (Albers 2011)	1 randomized controlled trial.pt.	346297
	2 controlled clinical trial.pt.	85685
	3 randomized.ab.	264003
	4 placebo.ab.	143018
	5 drug therapy.fs.	1598414
	6 randomly.ab.	192250
	7 trial.ab.	272618
	8 groups.ab.	1241006
	9 or/1-8	3094847
	10 (animals not (animals and humans)).sh.	3707170
	11 9 not 10	**2647129**
Platinum derivates: oxaliplatin, cisplatin, carboplatin (Albers 2011)	12 cisplatin/ae, tu, to (Suche nach Subheadings Adverse events, therapeutic use und toxicity)	14861
	13 cisplatin.tw. (Suche nach Textwörtern)	38332
	14 cis-diamminedichloroplatinum.tw.	2036
	15 platinum compounds.tw. or platinum compounds/ae, to, tu	1433
	16 exp organoplatinum compounds/ae, to, tu	6547
	17 (oxaliplatin or carboplatin).tw.	14183
	18 or/12-17	**55499**
Taxanes: docetaxel, paclitaxel, cabazitaxel (Albers 2011 angepasst)	19 paclitaxel/ae, tu, to	6164
	20 paclitaxel.tw	16400
	21docetaxel or cabazitaxel/ae, tu, to	8741

Structure	Search strategy	Hits
	22 (docetaxel or cabazitaxel).tw	7761
	23 taxane compounds.tw. or taxane compounds /ae, to, tu	13
	24 exp taxoids	23274
	25 or /19-24	**29394**
Other agents (search for in-text words		
	26 Vinca alkoid$.tw (0 Treffer), ersetzt durch bortezomib$.tw	3604
	27 (Vincristin$ or Vinorelbin$ or Vinblastin$).tw	24310
	28 Exp vincristine	19705
	29 Exp vinblastine (er sigt noch 2 Unterbefriffe unter Vinca alkoide)	11310
	30 Lenalidomid$.tw	1559
	31 Thalidomid$.tw	5885
	32 Eribulin$.tw	101
	33 Epothilon$.tw	711
	34 or/26-33	**48174**
	39 18 or 25 or 34	118 457
Neuropathies (Albers 2011)		
	35 exp peripheral nervous system diseases/ci, pc	6907
	36 exp central nervous system diseases/ci, pc	89868
	37 (neuropath$ or neuro$ or nerv$).tw.	1481721
	38 or/35-37	**1547221**
Supportive therapies		
	40 exp neuroprotective agents/	58201
	41 chemoprotect$.mp.	1221
	42 Protective Agents/	3221
	43 neuroprotective agents/	20352
	44 (protect$ or neuroprotect$).tw.	502339
	45 (ORG2766 or ORG 2766).tw.	219
	46 Adrenocorticotropic Hormone/	43427
	47 (acth or corticotropin or corticotrophin or adrenocorticotropin or adrenocorticotrophin).tw.	44141
	48 glutathione/ or glutathione.tw.	95545
	49 amifostine.tw. or amifostine/	1627
	50 exp nerve growth factors/	35651
	51 (nerve adj3 growth adj3 factor$).tw.	14959
	52 neurotrophin 3.tw.	2081
	53 exp antidotes/	48201
	54 antidote$.tw.	3743
	55 vitamin E.tw. or vitamin E/	30745
	56 (alc or acetyl l carnitine).tw.	1795
	57 Acetylcarnitine/	999
	58 Calcium$.tw	278706
	59 magnesium$.tw	41402
	60 Duloxetin$.tw	1314
	61 Menthol or Peppermint or Scrambler.tw	2708
	61 alpha$ lipoic$ acid$.tw	1313
	63 Carbamazepine$.tw	10927
	64 Gabapentin$.tw	3752
	65 pregabalin$ or valproat$.tw	8612
	66 venlafaxin$.tw	2586
	67 Lamotrigin$.tw	3561

Structure	Search strategy	Hits
	68 Lidocain$.tw	16448
	69 Fluoxetin$.tw	8714
	70 Topiramat$.tw	2876
	71 Amitriptylin$.tw	5453
	72 oxycodone$.tw	1489
	73 Capsaicin$.tw	10440
	74 or/40-73	**1131070**
Summary	**75 11 and 39 and 38 and 74**	**501**

Central Search on April 4th 2013

Strategy	Hits
#1(cisplatin OR cis-diaminedichloroplatinum OR platinum OR organoplatinum OR oxaliplatin OR carboplatin)	9095
#2 (paclitaxel OR docetaxel OR cabazitaxel OR taxan* OR toxoid*)	4752
#3 (vinca alkoid* OR vincristin* OR vinorelbin* OR vinblastin*)	4372
#4 (bortezomib OR lenalidomid* OR thalidomide* OR eribulin* OR epothilon*)	837
#5 (#1 OR #2 OR #3 OR #4)	15774
#6 (therap* OR adverse OR toxic* OR neurotoxic*)	393816
#7 (#5 AND #6) Adverse events of chemotherapies	11702
#8 MeSH descriptor Acetylcarnitine, this term only	6
#9 (acetyl l carnitine) or alc	230
#10 (calcium* OR magnesium* OR duloxetine* OR menthol* OR peppermint* OR Scrambler*)	18432
#11 (alpha* lipoic* acid*)	154
#12 (carbamazepin* OR gabapentin* pregabalin* OR valproat* OR venlafaxin* OR lamotrigin* OR lidocain* OR fluoxetine* topiramat* OR amitriptylin* OR oxycodon* OR capsaicin*)	12647
#13 (neuroprotect* OR chemoprotect* OR protect* OR org2766 OR corticotrop* OR glutathione OR amifostine OR (growth NEXT factor*) OR neurotrophin3 OR neurotropin3 OR antidote* OR (vitamin NEXT E))	28442
#14 (#8 OR #9 OR #10 OR #11 OR #12 OR #13) supportive therapies	57712
#15 (neuropath* OR nerv* OR neurotox* OR neurol*)	48228
#16 MeSH descriptor Peripheral Nervous System Diseases, this term only	117
#17 MeSH descriptor Peripheral Nerves, this term only	153
#18 (#15 OR #16 OR #17) neurotoxicities	48228
#19 (#7 AND #14 AND #18)	250

Appendix 2: CEBM levels of evidence

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR" validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR" with 1b studies from different clinical centers	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval"¡)	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population	Validating** cohort study with good" " " reference standards; or CDR" tested within one clinical center	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts" "	All or none case-series	Absolute better-value or worse-value analyses " " " "
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR" or validated on	Exploratory** cohort study with good" " " reference standards; CDR" after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and

		split-sample§§§ only			including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Appendix 3: SIGN levels of evidence

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Appendix 4: Tables of Evidence for prevention of CIPN

Cisplatin

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Alpha-lipoic acid								
Guo 2013 Full text	RCT Single-center 2 arms n=243 USA	**Patients scheduled to receive cisplatin- or oxaliplatin-based regimens.** **Age:** Arm A: 55 (±11), Arm B: 57±12 **Sex m/f:** Arm A: 54/46%, Arm B: 52/48% **CTX:** **Cisplatin-** based regimens Stratified into a) no cisplatin b) patients receiving < 399mg/m^2 c) patients receiving >400	Arm A: **ALA** 600mg 3xdaily n=122 Arm B: Placebo n=121	**Primary outcomes:** ***Patient assessments:*** FACT/GOG-NTX NCI-CTC **Secondary outcomes:** ***Questionnaire:*** BPI ***Clinical assessments:*** Timed functional tests (Six-hole button test, Fifty-foot walk test, coins test)	**24±4 weeks:** **Neurotoxicity:** **NCI-CTC:** Arm A: **Grade 1-2:** 27/34 (79,4%) **Grade 3-4:** 3/34 (0,9%) Arm B: **Grade 1-2:** 27/36 (75%) **Grade 3-4:** 5/36 (13,8%) (all p>0.05) **FACT/GOG-NTX-Score:** Arm A: Baseline: 3.7±5.1 24 weeks: 9.6±7.6 Arm B: Baseline: 3.0±4.1 24 weeks: 9.7±8.1 (p>0.05) **BPI-score:** Arm A: Pain worst: Baseline: 1.8±3.1 24 weeks: 2.4±3.4 Pain average: Baseline: 1.7±2.3	Complete response: 5 vs. 4 patients Completed 24 weeks: Arm A: 28% Arm B: 30% Drop-outs mainly due to withdrawal of consent (42 patients both groups) and patient non-compliance (18 vs. 15 patients)	ALA provided by Jarrow Formulas, Inc. Support by National Institute of Health through Cancer Center Support Grant, CA016672	**2B-** **1-** Randomization: yes (method unclear) Blinding: yes (method unclear) ITT: yes High drop out rates, low statistical power, early termination

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		mg/m^2 **Oxaliplatin-**based regimens Stratified into a) no oxaliplatin b) patients receiving <750 mg/m^2 c) patients receiving >750 mg/m^2			24 weeks: 1.9±2.4 Arm B: Pain worst: Baseline: 2.2.8±3.0 24 weeks: 1.9±2.9 Pain average: Baseline: 1.8±1.7 24 weeks: 1.3±1.6 (p>0.05) **Functional tests:** Six-hole button test: Arm A: Baseline: 28±16 24 weeks: 32±19 Arm B: Baseline: 33±33 24 weeks: 29±15 Fifty-foot walk test: Arm A: Baseline: 17±14 24 weeks: 17±11 Arm B: Baseline: 20±27 24 weeks: 15±6 Coins test: Arm A: Baseline: 6±4 24 weeks: 6±2 Arm B: Baseline: 6±3 24 weeks: 6±2 (p>0.05)			
Albers 2011 Full text	Systematic Review Search	**Patients undergoing CTX with cisplatin**	Arm A: **Org 2766 Amifostine**	See below	See below	See below	None	**1 A** **1++**

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	up to 08/10 Including following RCTs for Cisplatin: Argyriou 2006 Bogliun 1996 Cascinu 1995 Gandara 1995 Hovestadt 1992 Kemp 1996 Pace 2003 Planting 1999 Roberts 1997 Schmidinger 2000 Smyth 1997 Van	Age: ≥18 Sex: either sex CTX: **Cisplatin-**based regimens (85mg/m^2 or 100 mg/m^2)	**DDTC GSH Mg Sulfate Sub carbonate Vitamin E** Arm B: Placebo or no treatment					

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	Gerven 1994 Van-der-Hoop 1990							
ACTH (4-9) Analogue: Org 2766								
Roberts 1997 (Albers 2011)	RCT multi-center 2 arms n=196 USA	**Ovarian cancer** Sex m/f: 0/100% CTX: **Cisplatin** (75 to100 mg/m^2) + Cyclophosphamide (600 - 1000mg/m^2)	Arm A_1: **Org 2766** (2mg/kg , n=53) Arm A_2: **Org 2766** (4 mg/kg, n=57) before and one hour after cisplatin n=129 Arm B: placebo n=67	**Primary outcome:** ***Semi-quantitative testing:*** Vibration Perception Threshold (VPT) **Secondary outcome:** No data.	**Vibration Perception Threshold:** Arm A1+A2: 2.81 ± 1.42 vs. placebo:2.56 ±1.89 % receiving sufficient CTX: A1: 54/63 (85%), A2: 50/66 (75%) vs. 53/67 (79%) VPT increased during the study, independent of receiving Org 2766, with no difference in the rate of change or the degree of neuropathy.	No data for OS, PFS, DFS, TR. Progression of disease was similar in the Org 2766 and control groups after an average of 24 months of follow-up.	No financial source reported.	**1B-** **1+** Randomization: method unclear Blinding: observer and outcome unclear ITT: no Notes: Allocation concealment unclear.
Van Gerven 1994 (Albers 2011)	RCT Single-center 2 arms n=42	**Testicular + Adeno-carcinoma** Sex m/f: 100/0%	Arm A: **Org 2766** (2mg/d x 5 days) n=19	**Primary outcome:** ***Semi-quantitative testings:*** Vibration Perception	**Vibration Perception Treshold:** Arm A: 1.85 ±1.87 Arm B:4.03 ± 5.06 Risk Ratio 3-5 month after treatment:	No data for OS, PFS, DFS, TR. Total	Study drug pro-vided by Organon Internation	**2B-** **1-** Randomization: method unclear

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	Netherlands	CTX: **Cisplatin** (100mg/m^2 , at least 4 cycles) + different combinations of etoposide, bleomycin + ifosphamide	Arm B: placebo n=23	Treshold (VPT) **Secondary outcome:** ***Clinical assessments:*** Usage of non validated neuro-logical scales, no statistical com-parison performed.	RR: 0.67; 95% CI:0.31-1.43	cumulative amount of cisplatin (mg/m^2): Arm A: 436 (SD 101) Arm B: 474 (SD 151)	al, Oss, The Nether-lands, no other finanial source reported.	Blinding: unclear ITT: no Notes: Very small numer of participants.

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Hovestadt 1992 (Albers 2011)	RCT 2 arms n=18 Netherlands	**Ovarian cancer** Sex m/f: 0/100% CTX: **Cisplatin** (75 mg/m^2) + Cyclo-phosphamide (750mg/m^2) up to 9 cycles.	Arm A_1: **Org 2267** (1mg/m^{2}s.c. 24 h before and after cisplatin) Arm A_2: **Org 2766** (0.25 mg/kg) n=7 Arm B: placebo n=11	**Primary outcome:** ***Semi-quantitative testing:*** Vibration Perception Treshold (VPT) **Secondary outcome:** ***Clinical assessments:*** Usage of non validated neurological scales, no statistical comparison was performed.	**Vibration Perception Treshold:** Mean after 1 month: Arm A_1: 1.1 Arm A_2: 2.9 Arm B: 3.7 Mean after 4 months: Arm A_1: 2.5 Arm A_2: 14.6 Arm B:: 8.1 Mean after 4-12 months: Arm A_1: 2.0 Arm A_2: 3.6 Arm B: 4.8 Mean after 12-24 months: Arm A_1: 0.8 Arm A_2: 0.6 Arm B: 2.9 No CI or p-value reported. Drop outs: 9/18 (50%) No reasons stated.	No data for OS, PFS, DFS, TR.	No financial source reported.	**2B-** **1-** Randomization: method unclear Blinding: yes, but observer blinding unclear Notes: Very small number of participants. Dropout 50%

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Van der Hoop 1990. NEJM (Albers 2011)	RCT Single-center 2 arms n= 55 Netherlands	**Ovarian cancer** Sex m/f: 0/100% CTX: **Cisplatin** (75 mg/m^2)+ Cyclo-phosphamide (750mg/m^2) up to 9 cycles.	Arm A_1: **Org 2267** (1mg/m^2 s.c., 24 h before and after cisplatin n= 16 Arm A_2: **Org 2267** (0.25 mg/m^2 s.c., 24 h before and after cisplatin n= 17 Arm B: placebo n=22	**Primary outcome:** ***Semi-quantitative testing:*** Vibration Perception Treshold (VPT) **Secondary outcome:** ***Clinical assessments:*** Neurological examination evaluated after 4+ 6 CTX courses, resulting in a "sumscore."	**Vibration Perception Treshold:** Mean after 4th cycle: Arm A_1: 0.50 Arm B: 1.61 (p<0.005) Mean after 6th cycle: Arm A_1: 0.66 Arm B: 5.87 (p<0.005) Administration of low-dose Org 2267 had no effect.	No data for OS, PFS, DFS, TR.		**2B-** **1-** Randomization: yes Blinding: yes ITT: Notes: Very small number of participants. Adequacy of analyses inadequate
Amifostine								
Rick 2001	RCT Single-centre 2 arms	**Germ-cell tumors (GCT)** **Age:** Arm A: 35 Arm B: 32	Arm A: **Amifostine** (500mg) n=20		**Neurotoxicity** (NCI-CTCAE): TIPgroup Arm A: Grade 1-2: 12/20 (60%) Grade 3: 1/20 (5%) Arm B:	**CR, PRm- or PRm+:** 15 of 17 (85%) vs. 13 of 15 (86%)	No financial source reported.	**2B** **1-** Blinding: no ITT: no data

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	n=40 Germany	**Sex: no data** **CTX:** **Cisplatin** (100-1100 mg/m2 cumulative) + **Paclitaxel** +ifosfamide, 3 cycles (=TIP)+ followed by 1cycle of high-dose CET (**Carboplatin**, etoposide and thiotepa)	Arm B: No treatment. n=20		Grade 1-2: 14/20 (70%) Grade 3: 3/20 (15%) Grade 4: 1/20 (5%) After 12 weeks: Arm A: Grade 1-2: 10/14 (70%) Grade 3: 2/14 (14%) Arm B: Grade 1-2: 9/14 (63%) Grade 3: 1/14 (7%) Grade 4: 3/14 (21%) Drop outs: progressive tumor: 3 severe complications during TIP: 2 early death: 1 patient refusal: 2			Notes: Small sample size.
Planting 1999, Ann Oncol (Albers 2011)	RCT Single-centre 2 arms n=74 Netherlands	**Head and neck cancer** Sex: either sex CTX: **Cisplatin** (70 mg/m^2 weekly) up to 6 cycles.	Arm A: **Amifostine** (740 mg/m^2 before cisplatin) n=37 Arm B: Placebo n=37	**Primary outcome:** ***Semi-quantitative testing:*** Vibration Perception Treshold (VPT) recordings. **Secondary outcome:** ***Patient assessments:*** NCI-CTCAE	**Vibration Perception Treshold:** at 3 month Mean increase left hand: Arm A: 0.15 vs. Arm B: 0.48 (MD 0.33, CI95% (-0.01- 0.67) Mean increase right hand: 0.18 vs. 0.40 (MD 0.12, CI95% (-0.03- 0.27) Completion of six cycles: 28/37 (76%) vs. 20/36 (56%) patients (p= 0.07)	**CR** Arm A: 6.7% Arm B: ? **PR** Arm A: 53% Arm B: 46%	Amifostine was supplied by USB Pharma Ltd. Watford.	**2B** **1-** Randomization: method unclear Blinding: inadequate ITT: no data Notes:

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
					Completion without delay: 15/36 (42%) vs. 20/37 (54%) **Neurotoxicity** NCI-CTC: Grade 1: 4/37 (11%) vs. 5/37 (14%) (RR 0.80; 95%CI 0.23-2.75) Adverse effects: Hypotension 17/36 (47%) patients			
Kemp 1996 (Albers 2011)	RCT Single-centre 2 arms n=242 USA	**Ovarian cancer** **Sex** m/f: 0/100% **CTX:** **Cisplatin** (100 mg/m^2) + Cyclo-phosphamide (1000 mg/m^2) every 3 weeks x 6 cycles.	Arm A: **Amifostine** (910 mg/m^2 pretreatment) n=122 Arm B: No treatment n=120	**Primary outcome:** None reported. **Secondary outcome:** ***Patient assessments:*** NCI-CTCAE	**Neurotoxicity** (NCI-CTCAE): Grade 1,2,3: Arm A: 67/122 (55%) Arm B: 81/120 (68%), p=0.029 RR: 0.81; 95%CI (0.66-1.00) (p=0.047) Discontinuation of treatment due to neurologic toxicity: 1/122 (0.8%) vs. 2/120 (1.7%) **Adverse effects:** Transient hypotension: Arm A: 75/122 (62%) Emesis: 96% vs. 88%	**OS** Arm A: 122 month Arm B: 120 month p= 0.87 **CR** Arm A: 26/60 (43.3%) Arm B: 19/52 (36.5%) Difference; 6.8 95%CI: (-11.3-24.9) No reduction of the antitumor-efficacy of	No financial source reported.	**1B-** **1-** Randomization: method unclear ITT: no data Blinding: no

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
						cisplatin.		
Diethyldithiocarbamate (DDTC)								
Gandara 1995, JCO (Albers 2011)	RCT multi-centre 2 arms, n= 214 USA 04/90-02/92	**Ovarian cancer, Small cell-lung cancer + non-small cell-lung cancer** **Age:** Arm A: 57(28-75) Arm B: 57 (22-78) **Sex:** either sex	Arm A: **DDTC** (1.6 g/m^2, 15 min before CTX) n=106 Arm B: placebo n=108	***Primary outcome:*** No data **Secondary outcomes:** ***Patient assessment:*** NCI-CTCAE	**Neuropathy** (grade ≥3, NCT-CTCAE): 13/96 (13%) vs.12/99 (12%) (RR: 1.12, 95% CI 0.54 to 2.32), (p>0.05) **Withdrawels for CTX-induced toxicity:** 22/96 (23%) vs. 9 /99 (9%) (p=0.008) **Adverse experiences:** 90/96 (94%) vs. 92/99 (93%)	No data for OS, PFS, DFS. Response rates: 47/96 (49%) vs. 43/99 (43%)	No financial source reported.	**1B-** **1-** Randomization: method unclear Blinding: yes Notes: high number of drop outs, A blinded interim safety analysis led to

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		CTX: **Cisplatin** (100 mg/m^2) + Etoposide (100 mg/m^2)or cyclo-phos-phamide (750 mg/m^2) for 6 cycles			**Severe adverse experiences:** 30/96 (31%) vs. 27/99 (27%) **Withdrawal:** **Arm A:** 74% **Arm B:** 40.4% P<0.001			unblinding of treatment arms and suspension of further patient accural.
Glutathione (GSH)								
Schmidinger 2000 (Albers 2011)	RCT single-centre, 2 arms n=20 Austria	**Non-small cell lung cancer or head- and neck cancer** **Sex:** either sex **CTX:** **Cisplatin** (80 mg/m^2) + etoposide or 5-fluorouracil	Arm A: **GSH** (5g/m^2 before CTX) n=11 Arm B: Placebo n=9	**Primary outcome:** None reported. **Secondary outcome:** ***Patient assessment:*** WHO- toxitcity grade criteria	**Neurotoxicity** (WHO): No change in WHO- neurotoxicity was noted.	**Median OS:** 13.1 vs.10.5 months **Median PFS**: 6.6. Vs. 7.2 months Response: 6/11 (54%) vs. 4/8 (50%)	Not reported.	**2B** **1-** Randomization: method unclear Blinding: out-come blinding unclear Notes: Very small sample size

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Smyth 1997 (Albers 2011)	RCT single-centre 2 arms n=151 UK	**Ovarian cancer** **Sex** m/f: 0/100% **CTX:** **Cisplatin** (100 mg/m^2) for 6 cycles	Arm A: **GSH** (3g/m^2 before CTX) n=74 Arm B: Placebo n=77	**Primary oucome:** None reported. **Secondary outcome:** ***Patient assessments:*** NCI-CTCAE QoL- Quality of Life. Hospital Anxiety and Depression Scale (HAD). Rotterdam Scales.	**Neurotoxicity** (NCI-CTCAE): All Grades: Arm A: 39% Arm B: 49% Grade 1: Arm A: 24/74 (32%) Arm B: 32/77 (42%) Grade 2: Arm A: 5/74 (7%) Arm B: 4/77 (5%) Grade 3: Arm A: 0 Arm B: 2/77 (3%) No CI or p-value reported. **Proportion of patients receiving Cisplatin** (100 mg/m2) for 6 cycles: 17/74 (23%) vs. 12/77 (15%),p 0,04 **Hospital Anxiety +Depression Score:** mean maximum increase 0.8 vs. 2.5 in favor for GSH **Rotterdam scores:** Arm A: 45/47 (96%) had better scores **QoL:** Patients reported an improvement of QoL in the intervention group.	**Response:** 30/41 (73%) vs. 24/39 (62%) No data for OS, PFS, DFS, TR.	Boehringer Mann-heim UK + Boehringer Mann-heim Italy	**1B-** **1-** Randomization: method deemed secure Blinding: unclear Notes: Adequacy of analyses deemed adequate.
Bogliun 1996 (Albers	RCT single centre	**Ovarian cancer** **Sex** m/f: 07100%	Arm A: **GSH** (2.5 g	**Primary outcome:** ***Semi-quantitative***	**NDS** change >12 points: Arm A: 5/19 (26%) Arm B: 8/16 (50%)	No data for OS, PFS, DFS, TR.	Not reported.	**2B** **1-** Randomization:

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
2011)	2 arms n=54 Italy 09/92-07/94	**CTX: Cisplatin** (50 mg/m^2 for 9 cycles or 75 mg/m^2 for 6 cycles)	before CTX) n=27 Arm B: Placebo n=27	***assessments:*** VPT **Secondary outcome:** ***Neuro-physiological assessments:*** SNAP ***Clinical assessments:*** Neurological Disability Score (NDS) Neuropathy symptoms (NSS)	RR: 0.53; 95%CI (0.21-1.29) **NSS:** Arm A: 14/19 (74%) Arm B; 16/16 (100%) RR: 0.75, CI95% (0.56 to 0.99) **Vibration Perception Threshold:** Arm A: 2-3 fold increase Arm B: 7-1 fold increase **SNAP** decrease compared to base line: Arm A: 58 to 68% Arm B: 12 to 35% No statistics used.			Method unclear Blinding: unclear Notes: Adequacy of analyses deemed adequate. Small number of participants.
Cascinu 1995 (Albers 2011)	RCT Single-centre 2 arms n=50 Italy	**Gastric cancer** **Sex:** either sex **CTX: Cisplatin** (40 mg/m^2 9 cycles)	Arm A: **GSH** (1.5 g/m^2 before CTX) n=25 Arm B: Placebo n=25	**Primary outcome:** None reported. **Secondary outcome:** ***Neuro-physiological assessments:*** SNAP ***Patient assessments:*** WHO- toxitcity grade criteria	**SNAP:** Sural SNAP decrease: Arm A: 10.78 ± 5.84µv to 8.95 ±6.48 µv Arm B: 13.26± 4.1 µv to 7.92 ±1.68µv **Neurotoxicity** (WHO criteria): All Grades: Arm A: 4/24 (16%) Arm B: 16/18 (88%) Grade 1: Arm A: 3/24 (13%) Arm B: 3/18 (16%) Grade 2: Arm A: 1/24 (4%)	No data for OS, PFS, DFS, TR.	Not reported.	**2B** **1-** Randomization: method deemed secure Blinding: yes Notes:Small number of participants Adequacy of anayses

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
					Arm B: 10/18 (55%) Grade 3: Arm A: 0/24 Arm B: 2/18 (11%) RR: 0.13, CI 95% (0.02-0.47)			deemed adequate.
Colombo 1995 Full text	RCT Phase II Single-center 2 arms n=33 Italy 03/90-02/92	**Ovarian cancer** **Age:** Arm A: 56±9.68 Arm B: 52±9.52 **Sex** m/f: 0/100% **CTX:** **Cisplatin** (cumulative dose 450-650 mg /m^2, 50 mg/m^2/week, 9 cycles)	Arm A: **GSH** (2.5 g/m^2 before CTX) n=16 Arm B: No treatment n=17	**Electrophysiologic measures:** Sural SNAP Median SNAP Ulnar SNAP	**Neurotoxicity at nine weeks:** **Sural SNAP:** Arm A: Baseline: 13.05±8.18 Final : 9.65±5.9 Arm B: Baseline: 13.16±8.54 Final : 7.58±3.3	**Complete response:** Arm A: 7/16 Arm B: 4/16 **Partial response:** Arm A: 4/15 Arm B: 5/15 **Full dose received:** Arm A: 9/16 Arm B: 4/15	GSH by Boehringer Mann-heim	**2B** **1-** Randomization: Yes, method unclear Blinding: no Notes: small sample size
Magnesium sulfate and Magnesium subcarbonate								
Bodnar 2008 Full text	RCT single – centre 2 arms n= 41 Poland 01/03-	**Ovarian cancer** **Age:** Arm A:53(50-56) Arm B:54(46-56) **Sex** m/f: 0/100% **CTX:** **Paclitaxel** (135 mg/m^2) on day 1	Arm A: **Magnesium sulfate + Magnesium carbonate** n=20 Arm B:	**Toxicity assessment:** NCI-CTCAE	**Neurotoxicity** (NCI-CTCAE)**:** Arm A: **Sensory neuropathy:** Grade 1: 14/20 (70%) Grade 2: 3/20 (15%) Grade 3. 1/20 (5%) (p=0.49) **Motor neuropathy:** Grade 1: 12/20 (60%) Grade 2: 3/20 (15%) Grade 3. 1/20 (5%) (p=0.25)	Median TTP: ArmA. 20.9 Arm B: 14.8 (p=0.78) No difference in OS.	Military Institute of Health Services	**2B** **1-** Randomization: Yes, method unclear Blinding: yes Notes: Small sample

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	01/06	followed by **Cisplatin** (75 mg/m^2) for 6 cycles.	placebo n=21		Arm B: **Sensory neuropathy:** Grade 1: 11/20 (55%) Grade 2: 3/20 (15%) (p=0.49) **Motor neuropathy:** Grade 1: 11/20 (55%) Grade 2: 3/20 (15%) (p=0.25)			size. Investigating renal function not neurotoxicity Notes: -effects of cisplatin versus paclitaxel cannot be differentiated
Nimodipine								
Cassidy 1998 Full text	RCT Multi-centre 2 arms n=51 UK	**Ovarian Cancer** **Age:** Arm A: 57.2±8.1 Arm B: 52.7±11.4 **Sex** m/f: 0/100% **CTX:** **Cisplatin (**100mg/m^2) cyclophosphamide (705mg/m^2) for 6 cycles	Arm A: **Nimodipine** Orally 30-90mg up to 4/day n=24 Arm B: Placebo n=26	**Primary outcome:** WHO grading Neurotoxicity score 0-17, one count for each symptom **Secondary outcome:** Other toxicities NCI-CTCAE Tumor progression	**Neurotoxicity score:** Week 27 (n=40): Arm A: 10.4 (1.0) Arm B: 6.4 (0.8) p=0.002 **Neurotoxicity was worse in the intervention arm!** **Drop outs:** n=11 due to death, incomplete questionnaires etc. No significant differences between groups	Other toxicities: High incidence of nausea and vomiting in both groups. Only 24 patients continued Nimodipine after last CTX cycle	Bayer Uk limited	**2B-** **1-** Randomization: Yes, method unclear Blinding: observers and personnel not blinded ITT: no data Notes: High drop out due to nausea and vomiting

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Vitamin E								
Pace 2010 Full text	RCT Multi-center 2 arms n=108 Italy 08/04-07/07	**Varierty of solid tumors treated with cisplatin-regimes.** **Age:** Arm A:58(28-71) Arm B:58.5 (32-74) **Sex** m/f: 61/39% **CTX: Cispatin-**based regimes. (cumulative dose > 300 mg/m^2).	Arm A: **Vitamin E** (300 mg/day) n=54 Arm B: Placebo n=54	**Primary outcome:** Incidence of neurotoxicity **Secondary outcomes:** TNS Neurological examination, ***Electro-physiologic measures:*** Sural SNAP Median SNAP	**After 6 cycles:** **Neurotoxicity** (TNS): Grade >3: Arm A: 1/17 (5.9%) Arm B: 10/24 (41.7%) (p<0.01) **Sural SNAP:** Arm A: Baseline: 18.3±9.9 µV After CTX: 14.4±7.1 µV (p<0.05) Arm B: Baseline: 23.8±13.9 After CTX: 18.3±12.8 (p<0.01) **Reflexes + distal paraesthesia:** Arm A: Baseline: 0/17 After CTX: 6/17 (35%) Arm B: Baseline: 0/244 After CTX: 13/24 (54%)	Drop outs: -38 interrupted therapy due to disease progression -27 received less than 300 mg/m^2 cisplatin No data for PFS, DFS, OS etc.	Vit E by Rigentex, Italy, Ital-farmaco, Schering Plough Corp., Bayer, Sanofi-Aventis, Roche, support by Italian National Health System	**1B-2B** Randomization: yes, method unclear Blinding: yes ITT: no Notes: High rate of drop-outs
Argyriou 2006 (Albers 2011)	RCT single centre 2 arms n=35 Greece 03/03-03/04	**Variety of cancers** **CTX: Cisplatin**- based regimens for 6 cycles + other CTX-agents (including	Arm A: **Vitamin E** (600 mg/d) n=14 Arm B: No	**Primary outcome:** Not reported. **Secondary outcome:** ***Neuro-physiological assessments:*** Sensory response amplitudes (SNAP)	**SNAP:** Sural SNAP, superficial peroneal + ulnar SNAP showed a significant decline in Arm B relative to Vit E group. **Neurotoxicity** (examination): Arm A: 3/ 14 (21%) vs. Arm B: 11/16 (69%)	No data for OS, PFS, DFS, TR.	Not reported.	**2b** **1 -** Randomization: method unclear Blinding: no ITT: yes

Reference	Type of study mono vs. multi-center, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Control (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		5 who received docetaxel).	treatment n=16	***Patient assessments:*** Not specified PNP-score ***Clinical assessment:*** Neurological examination	(p= 0.03) **PNP score:** Arm A: 4.99 ± 1.33 vs. Arm B: 10.47 ± 10.62 (p = 0.023) Drop outs: Death: 3 Disese progression: 5			Notes: Very small number of participants.
Pace 2003 (aus Albers 2011)	RCT single centre 2 arms n=47 Italy 04/99-10/02	**Various solid tumors** **Sex:** either sex **CTX: Cisplatin** (cumulative dose > 300 mg/m^2).	Arm A: **Vitamin E** (300 mg/day) n=13 Arm B: No treatment n=14	**Primary outcome:** Not reported. **Secondary outcome:** ***Neuro-physiological assessments:*** Sensory reponse amplitudes (SNAP) ***Patient assessments:*** Modified Total Neuropathy Score (TNS) ***Clinical assessments:*** Clinical impairment (no validated scale).	**SNAP** Median SNAP: Arm A: Baseline: 15.5 ± 6.3 µv 6 months later : 13.7 ± 5.5 µv Arm B: Baseline: 14.5 ± 8.5 µv 6 months later: 13.6 ± 9.2 µv Sural SNAP Arm A vs. Arm B not significant. **TNS** (modified): Arm A: 4/13 (31%) Arm B: 12/14 (86%) RR:0.36; 95%CI (0.15-0.83) Severity of neuropathy was higher in Arm B than in Arm A, (4.7 vs. 2.0, p<0.01) 20 dropouts due to disease progression. 43%	**CR+ PR:** 61.5% vs. 72.7%	Not reported.	**2B-** **1-** Randomization: Method unclear Blinding: no Small number of participants, analysis is restricted to patients who received a cumulative dose of cisplatin >300mg/m^2 Drop outs: 43%

Oxaliplatin

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Alpha-lipoic acid								
Guo 2013 Full text	RCT Single-center 2 arms n=243 USA	**Patients scheduled to receive cispatin-or oxaliplatin-based regimens.** **Age:** Arm A: 55 (±11), Arm B: 57±12 **Sex m/f:** Arm A: 54/46%, Arm B: 52/48% **CTX: Cisplatin-**based regimens Stratified into a) no cisplatin b) patients receiving < 399mg/m^2 c) patients receiving >400 mg/m^2	Arm A: **ALA** 600mg 3xdaily n=122 Arm B: Placebo n=121	**Primary outcomes:** ***Patient assessments:*** FACT/GOG-NTX NCI-CTC **Secondary outcomes:** ***Questionnaire:*** BPI ***Clinical assessments:*** Timed functional tests (Six-hole button test, Fifty-foot walk test, coins test)	**24±4 weeks:** **Neurotoxicity:** **NCI-CTC:** Arm A: **Grade 1-2:** 27/34 (79,4%) **Grade 3-4:** 3/34 (0,9%) Arm B: **Grade 1-2:** 27/36 (75%) **Grade 3-4:** 5/36 (13,8%) (all p>0.05) **FACT/GOG-NTX-Score:** Arm A: Baseline: 3.7±5.1 24 weeks: 9.6±7.6 Arm B: Baseline: 3.0±4.1 24 weeks: 9.7±8.1 (p>0.05) **BPI-score:** Arm A: Pain worst: Baseline: 1.8±3.1 24 weeks: 2.4±3.4 Pain average: Baseline: 1.7±2.3 24 weeks: 1.9±2.4 Arm B: Pain worst: Baseline: 2.2.8±3.0	Complete response: 5 vs. 4 patients Completed 24 weeks: Arm A: 28% Arm B: 30% Drop-outs mainly due to withdrawal of consent (42 patients both groups) and patient non-comliance (18 vs. 15 patients)	ALA provided by Jarrow Formulas, Inc. Support by National Institute of Health through Cancer Center Support Grant, CA016672	**2B-** **1-** Randomization: yes (method unclear) Blinding: yes (method unclear) ITT: yes High drop out rates, low statistical power, early termination

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		Oxaliplatin-based regimens Stratified into a) no oxaliplatin b) patients receiving <750 mg/m^2 c) patients receiving >750 mg/m^2			24 weeks: 1.9±2.9 Pain average: Baseline: 1.8±1.7 24 weeks: 1.3±1.6 (p>0.05) **Functional tests:** Six-hole button test: Arm A: Baseline: 28±16 24 weeks: 32±19 Arm B: Baseline: 33±33 24 weeks: 29±15 Fifty-foot walk test: Arm A: Baseline: 17±14 24 weeks: 17±11 Arm B: Baseline: 20±27 24 weeks: 15±6 Coins test: Arm A: Baseline: 6±4 24 weeks: 6±2 Arm B: Baseline: 6±3 24 weeks: 6±2 (p>0.05)			
Calcium/Magnesium								
Hochster 2014 Annals of Oncology	RCT Single-center 2x2 arms	**Colorectal Cancer** **Age:** Arm **IO** Ca/Mg: 67±12 Arm **IO** placebo:	Intermitting oxaliplatin arm **IO:** Alternating 8 cycles as below	**Primary outcome: TTF** Time to treatment failure of oxaliplatin **Secondary outcomes:**	**Neurotoxicity ≥ grade 2** (NCI-CTCAE): **Ca/Mg:** 15/110 **Placebo:** 15/69 RR: 0.67; 95%CI 0.35 to 1.30	**Median TTF:** IO: 5.7 (4.7-7.1) CO: 4.2 (3.7-5.5) HR 0.58;	None reported	Randomization yes Blinding: yes ITT: yes

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	n=353 USA 02/05-08/06	62 ±12 Arm **CO** Ca/Mg: 63 ±12 Arm **CO** placebo: 61 ±2 **CTX: Oxaliplatin-**based : modified FOLFOX7 plus bevacizumab	and 8 cycles of Bevacizumab withou oxaliplatin + **Ca/Mg** (n=35) +placebo (n=36) Continuous oxaliplatin arm **CO:** mFOLFOX + Bevacizumab every 2 weeks +**Ca/Mg** (n=35) +placebo (n=33)	**TTP** Time to tumor progression QoL AEs		95%CI 0.41 to 083 **Median PFS:** IO: 12.0 (8.3 to not estimable) CO: 7.4 (6.9 to not estimable) HR: 0,53; 95%CI 0.29 to 0.99		Notes: Trial closed early due to an interim analysis showing a harmful effect of Ca/Mg
Loprinzi 2013 Full text JCO 2014	RCT Phase III Single-center	**Colon cancer** **Age:** Arm A: 56 Arm B: 57 Arm C: 57	Arm A: Before +after CTX: **Calcium/ Magnesiu**	**Primary outcome:** ***Patient assessments:*** NCI-CTCAE **Secondary**	**Neurotoxicity** (NCI-CTCAE): Grade 2: Arm A: 43% Arm B: 46% Arm C: 45%	No data for OS, DFS, TR. No differences in toxicities.	Axel Grothey, Sanofi-aventis	**1B** **1+** Randomization: yes

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	3 arms n=353 USA 06/10-06/12	**Sex** m/f: 48/52% **CTX:** Curative. **Oxaliplatin-**based FOLFOX 4 or modified 6, (85mg/m^2), 12 cycles	**m** (1g each) n=118 Arm B: Before +after CTX: Placebo n=119 Arm C: Before CTX: **Calcium/ Magnesium** After CTX: Placebo n=116	**outcomes:** ***Patient assessments:*** EORTC-QLQ-CIPN 20 Oxaliplatin-specific neuropathy instrument. Acute neuropathy evaluation On a 0-10 score.	No significant differences between groups in time to grade 2 neuropathy (p=0.97) No significant differences between groups in terms of acute neuropathy evaluations. No significant differences between groups in terms of average oxaliplatin dose (p=0.11) No significant differences between groups in terms of percentage of patients receiving full oxaliplatin-dose (p=0.25)	Number of cycles: Arm A: 117 Arm B: 116 Arm C: 115 (p>0.05)		Blinding: yes ITT: yes
Wen 2012 Ann Oncol Inclusion of: **Grothey 2011prospective Gamelin**	Meta-analyses including **4 RCTs** (Gamelin 08 Ishibashi 2010 Chay	**Colorectal carcinoma** **Age**: ≥18 **Sex**: either sex **CTX.** Palliative or Curative.	Arm A: **Calcium+ Magnesium** (before + after oxali-platin) n=802	**Primary outcome:** ***Patient assessments:*** NCI-CTCAE **Secondary outcome:** Number of treatment cycles and total dose	**Acute Neurotoxicity III°:** Arm A < Arm B: OR=0.26 95% CI (0.11-0.62) Drop out- rate: Arm A < Arm B: OR 0.23 95% CI (0.10-0.55) **Cumulative neurotoxicity:**	**Response Rate:** OR=0.82 95% CI (0.61-1.10) No differences in Median PFS:MD= 0.71	Project of National Natural Science Foundation of China	**2A** **1+** Notes: includeds retrospective studies. High risk of bias in

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
2008 prospective (Abstract only) **Chay 2010 prospective** **Ishibashi 2010 prospective** Knijn 2011 retrospective Chaves 2011 retrospective Gamelin 2004 retrospective Full text	2010 Grothey 2011) + 3 retro-spective trials Search: 1950-02/12 n=1170 (RCT only: n=214) China	**Oxaliplatin** based	Arm B: Placebo or no treatment n=368	of oxaliplatin. Response rate. OS PFS Studies with at least one primary or secondary event were included.	Arm A < Arm B: OR=0.42 95% CI (0.27-0.65) **All results showed that for grade ≥2 –neurotoxicity Mg/Ca was beneficial.** No difference in results for neurotoxicity grade1 OR=0.86 95%CI (0.63-1.18) **Total cycles of oxaliplatin:** RCT: OR=0.79 95% CI (0.33-1.93) Retrospectives: OR= 0.82 95% CI (0.60-1.12) **Dose of cumulative oxaliplatin:** Arm A: MD: 246.73 mg/m^2 95% CI (3.01-490.45)	month 95% CI (-0.59-2.01) Median OS: MD= 0.1 month 95% CI (-0.41-0.61)		retrospective studies (author). Low risk of publication bias. Incluion of abstracts.
Wu 2012 (EJC) Inclusion of:	Systematic review+ meta-analyses including	**Colorectal Cancer** **Sex:** Either sex. **CTX:** Naive. **oxaliplatin**-	Arm A: **Calcium+ Magnesium** (before and after	***Patient assessments:*** NCI-CTCAE Oxaliplatin-specific scale (OSS)	**NCI-CTCAE overall:** ≥Grade 2: OR=0.53 95%CI (0.31-0.91) Grade 3: OR=0.62	**Tumor response rate** (=complete plus partial tumor response)**:**	Source of funding: None declared	**2A** **1+** 2 reviewers screened the data

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Grothey 2011prospective Ishibashi 2010 prospective **Chay 2010 prospective** Dong 2010 prospective (Abstract only) Gamelin 2004 retrospective Knijn 2011 retrospective Kono 2009 respective Full text	4 RCTs + 3 cohorts Search: Up to 08/11 n=1238 (RCT only n= 244) China	based (FOLFOX 4+6, mFOLFOX 6, XELOX + FUFOX; 85-130mg/m^2)	oxalipatin) n=772 Arm B: Placebo or no treatment n=401	Neurotoxicity Criteria of DEBIOP-HARM (DEB-NTC) Tumor response rate	95% CI (0.39 0.96) **! Only RCT data !** ≥Grade 2: OR=0.47 95%CI (0.0.22-1.00) (random- effects model)	RR=0.91 95% CI (0.78-1.06)		independently. Inclusion of cohort studies.
Grothey 2011 In Wen 2012 Wu 2012	RCT Phase III Single-center	**Colon cancer** **Age:**<65yrs 65%	Arm A: **Calcium/ Magnesium** (1 g each	***Patient assessments:*** NCI-CTCAE Oxaliplatin-specific-	**Neurotoxicity** (NCI-CTCAE): Grade 0-1: Arm A: 39/50 (78%) Arm B: 30/52 (58%) ≥Grade 2: Arm A: 11/50 (22%)	No data for OS, PFS, DFS, TR	Axel Grothey, Sanofi-Aventis	**1B** **1+** Randomization yes

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
In detail Full text *Journal of Clinical Oncology*	2 arms n=102 USA 01/06-06/07	**Sex** m/f: 53/47% **CTX:** adjuvant **Oxaliplatin**-based FOLFOX (4 or 6, 85mg/m^2)	before + after CTX) n=50 Arm B: Placebo n=52	score Meaning of neuropathy for patient on a 0-10 numeric score	Arm B: 21/52 (41%) (p=0.038) **Oxaliplatin-specific scale:** Grade 0-1: Arm A: 36/50 (72%) Arm B: 25/52 (49%) ≥Grade 2: Arm A: 14/50 (28%) Arm B: 26/52 (51%) (p=0.018) No differences in toxicities between the treatment arms (hypercalcaemia, hypermagnesemia). Drop outs: Patient refusal: 5 vs.3 Adverse effects: 8 vs.7 Other: 6 vs. 11		Steven R. Alberts, Bristol-Meyers-Squibb Charles L.Loprinzi, Sanofi-aventis	Blinding: yes ITT: yes Notes: Decreased statistical power.Early termination due to the publication of the CONCEPT trial (Grothey 2008).
Chay 2010 in Wen 2012 Wu 2012 In detail Full text	RCT Single-center 2 arms n=27 Singapore 10/05-06/07	**Colorectal cancer** **Age:** Arm A: 55 Arm B: 53 **Sex** m/f: 52/48% **CTX:** adjuvant **Oxaliplatin**-based FOLFOX 4 (85mg/m^2) or capecitabine + oxaliplatin (130	Arm A: **Calcium/ Magnesium** (1 g each before + after CTX) n=13 Arm B: Placebo n=14	**Primary outcomes:** ***Patient assessments:*** NCI-CTCAE Oxaliplatin-specific-score ***Electrophysiologic measures:*** Objective NCS including sural, ulnar, median and peroneal superficial SNAPs	**Neurotoxicity:** Acute Neuropathy: Arm A: 10/13 (77%) Arm B: 12/14 (86%) OR: 0.56, 95% CI 0.08-4.01 **NCI-CTCAE:** All grades: Arm A: 7/9 (78%) Arm B: 10/10 (100%) RR: 0.79, 95% CI 0.54-1.15 **OSS:** Cumulative neuropathy:	No interference of ca/mg infusion with oxaliplatin could be found. 13/27 patients completed 6 month CTX. No data for PFS, OS, TR etc.	Funding of $40 400 came from Sanofi-Snythelabo Pte Ltd Eloxatin Clinical Study Grant	**2B-** **1-** Randomization: method unclear Blinding: yes ITT: no data Notes: Early termination due to results of CONcePT trial

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		mg/m^2)			All Grades: 4/9 (36%) vs. 3/10 (30%) RR: 1.48, 95% CI 0.45-4.90 **Objective NCS median score:** End of treatment: Arm A: score 6/7 Arm B: sore 0/9 p=0.02 Study does not support the effect of ca/mg infusions.			Very small sample size
Dong 2010 Abstract only!	RCT Single-center 2 arms n=93 China 06-07	**Colorectal cancer** Arm A: 57.2±11.4 Arm B: 59.1±10.8 **Sex** m/f: 67/33% **CTX:** adjuvant **Oxaliplatin**-based FOLFOX 4 (85mg/m^2	Arm A: **Calcium/ Magnesium** (1 g each before + after CTX) n=31 Arm B: No therapy n=29	**Primary endpoints:** ***Patient assessments:*** NCI-CTCAE	**Neurotoxicity** (NCI-CTCAE): Arm A: Grade 1: 13 Grade 2: 2 Grade 3: 2 Arm B: Grade 1: 14 Grade 2: 9 Grade 3: 2	No data.		**2B-** **1-** Randomization: method unclear Blinding: no ITT: no data Notes: Very small sample size
Ishibashi 2010 In Wen 2012 Wu 2012	RCT Single-center	**Colorectal cancer** **Age:** Arm A:	Arm A: **Calcium/ Magnesium** (850 mg	**Primary endpoints:** ***Patient assessments:*** NCI-CTCAE Debiofarm	**Neurotoxicity:** DEB-NTS: Arm A: ≥Grade 1: 17 (100%) ≥Grade 2: 12 (71%)	**CR:** Arm A: 4/12 (33%) Arm B: 1/12 (8%)	None reported.	**2B** **1-** Randomization: yes

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Albers 2011 In detail Full text	2 arms n=33 Japan 04/05-09/06	63 (32-74) Arm B: 64 (35-73) **Sex** m/f:48/52% **CTX:** adjuvant **Oxaliplatin**-based FOLFOX 6 (85mg/m^2)	calcium gluconate, 720mg magnesium sulfate before + after CTX) n=17 Arm B: Placebo n=16	Neurotoxicity scale **Secondary endpoint:** Antitumor activity, PFS, plasma levels of platinum	≥Grade 3: 1 (6%) Arm B: ≥Grade 1: 15 (94%) ≥Grade 2: 9 (56%) ≥Grade 3: 0 NCI-CTCAE: Arm A: ≥Grade 1: 17 (100%) ≥Grade 2: 1 (6%) ≥Grade 3: 1 (6%) Arm B: ≥Grade 1: 15 (94%) ≥Grade 2: 1 (6%) ≥Grade 3: 0 All p-values >0.5	**PR:** Arm A: 4/12 (33%) Arm B: 4/12 (33%) **SD**Arm A: 4/12 (33%) Arm B: 3/12 (25%) **PFS:** Arm A: 9.2 month Arm B: 8.1 month (p=0.56)		Blinding: yes ITT: no data Notes: Early termination. Very small sample size
Gamelin 2008 In detail **Abstract only!!**	RCT Single-center 2 arms n=52 France	**Colorectal cancer** **Age:** Arm A: 63 (32-74) Arm B: 64 (35-73) **Sex** m/f:48/52% **CTX:** adjuvant **Oxaliplatin**-based FOLFOX 4 regimen, (85mg/m^2)	Arm A: **Calcium/ Magnesium** (1 g calcium gluconate, 1.5 g magnesium sulfate before + after CTX)n=26 Arm B: Placebo	***Patient assessments:*** Acute neuropathy Measured by NCI-CTCAE	**Neurotoxicity** (NCI-CTCAE): Arm A: 5% Arm B: 24% *P* < .001	Response rate: Arm A: 13/26 (50%) Arm B: 14/26 (54%) OR 0.86; 95%CI (0.29-2.55) **PFS:** Arm A:12 ± 0.6 Arm B:12 ± 0.5 *P* = .79 **OS:** Arm A:	Not reported.	**Letter to the editor in JCO. No full publication available.** Randomization, blinding, allocation concealment methods unclear

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
			n=26			25.1 ± 4 Arm B: 25.5 ± 4.1 *P* = .45		
Carbamazepine								
Von Delius 2006 Full text	RCT Multi-center 2 arms n=36 phase-II-study Germany	**Colorectal cancer** **Sex** m/f: 50/50% **Age:** Arm A: 62(36-77) Arm B: 64(38-82) **CTX:** Curative.Naive. **Oxaliplatin** (FUFOX: 85 mg/m^2+folinic acid+5-FU)	Arm A: **Carbama-zepine** (6 days before oxaliplatin, first dose 200mg i.v., stepwise elevated by 200mg, targeted plasma level: 4-6mg/l) n=19 Arm B: No Carbama-zepine n=17	**Primary outcome:** ***Patient assessments:*** Neurotoxicity grading scale of Levi **Secondary outcome:** ***Patient assessments:*** PNP score Anti-tumor efficacy	**Neurotoxicity** (Levi's scale): Grade: Arm A/Arm B: Grade1:8/19 (42%)vs. 7/17 (41%) Grade2:2/19 (11%) vs. 4/17 (24%) Grade3:3/19 (16%) vs. 4/17 (24%) Grade4:1/19 (5%) vs. 2/17 (12%) (p=0.46) **PNP score**: No difference in neurotoxicity. 11 % (2 patients) discontinued carbamazepine treatment due to dizziness, headache or nausea which disappeared after discontinuation of carbamazepine. **Early finish of CTX :** Arm A: 4/19 (21%) due to diarrhoea (2/19), resection of liver metastasis or thrombocytopenia. Arm B: 3/17 (18%) due to diarrhea, neurotoxicity or withdrawal of consent. **Mean number of cycles ± Standard Deviation:** Arm A: 3.16 ±2.09	**Median PFS:** Arm A: 6.0 months, 95% CI (3.2-8.9) Vs. : 7.2 months, 95% CI (5.4-9.0) **Median survival time:** 15.1 months, 95% CI (10.9-19.5) vs. 17.4 months 95% CI (4.8-30)	Grants from Sanofi-Aventis.	**2B** **1-** Randomization: yes Blinding: no ITT: yes Notes: Very small sample size

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
					Arm B: 3.29 ±1.57 p=0.83 **Mean cumulative dose of oxaliplatin ± SD:** Arm A: 611±508 mg/m^2 Arm B: 750±437 mg/m^2 p=0.71			
Ganglioside-monosialic acid								
Zhu 2013 Full text	RCT Single-center 2 arms n=120 China 12/10-12/11	**Gastric or Colorectal cancer** **Sex**m/f: 78/23% **Age:**55(21-74) Arm A/B: 55.10/ 54.83 **CTX: Oxaliplatin-**based XELOX (oxaliplatin 130mg/m^2 + capecitabine) FOLFOX4 (oxaliplatin 85mg/m^2 + leukovolin+ 5-FU	Arm A: **GM1** (First day of CTX: 100 mg once daily, before CTX administration for 3 days) n=60 Arm B: No GM1. n=60	***Patient assessments:*** NCI-Sanofi-Criteria	**Neurotoxicity:** Arm A/Arm B: 68/78% Grade 0: 19/60 (32%) vs.13/60 (22%) Grade 1: 20/60 (33%) vs.16/60 (27%) Grade 2: 16/60 (27%) vs.14/60 (23%) Grade 3: 5/60 (8%) vs.17/60 (28%) (p=0.021) 4 cases of severe allergy (3 Arm A, 1 Arm B). 2 patients underwent surgery and exhibited severe neurotoxic symptoms after surgery. 25% decreased visual acuity/hypogeusia (both groups)	**Median number of cycles:** Arm A: 5.88 (2-12) Arm B: 6.63 (3-12) (p=0.894, Cave bezieht sich nur auf die Zyklenanzahl) No data for OS, PFS, DFS, TR.	Not reported.	**1B** **1+** Randomization Yes Blinding: no ITT: no data

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Glutamine								
Wang 2007 Full text	RCT Single-center 2 arms n=86 China 09/04-12/05	**Metastatic Colorectal cancer** **Sex** m/f: 65/35% **Age**: Arm A: <50y: 43% ≥50y: 57% Arm B: <50y: 36% ≥50y: 64% **CTX:** Palliative Naive. **Oxaliplatin** (85 mg/m^2 on days 1and15; + FA+ 5-FU)	Arm A: **Glutamine** (15g 2/day for 7 days) n=42 Arm B: No Glutamine. n=44	***Patient assessments:*** NCI-CTC Activities of daily living. ***Electro-physiological assessments:*** Sensory amplitude potential (SAP) Nerve conduction velocity (NVC) Compound muscle action potential (CMAP).	**Neurotoxicity:** Arm A/Arm B: After six cycles Grade 0: 20/42 (48%) vs.12/44 (27%) Grade 1–2: 17/42 (41%) vs.18/44 (41%) Grade 3–4: 5/42 (12%) vs.14/44 (32%) (p=0.04) **Activities of daily living:** Arm A/Arm B: Interference: 7/18 (17/41%) No interference: 35/26 (83/60%) (p=0.02) **Oxaliplatin dose reduction:** Arm A/Arm B: 3/12 (7/21%) (p=0.02)	**Median OS:** 17.3 vs. 18.6 months (p=0.79) **Overall Response rates:** 22/42 (43%) vs. 21/44 (50%)	Taiwan Clinical Oncology Research Foundation. Grants from Taipei Veterans General Hospital.	**2B** **1-** Randomization: yes Blinding: no ITT: not reported
Glutathione (GSH)								
Milla 2009 (Albers 2011)	RCT Single-center	**Colorectal cancer** **Age:** 61 (44–75)	Arm A: **GSH** (1.5 mg/m^2) n=14	***Patient assessments:*** NCI-CTCAE	**Neurotoxicity (**NCI-CTC): Arm A: Grade 1: 7/14 (50%) Grade 2: 7/14 (50%) Arm B:	No data for OS, PFS, DFS **Median number of**	None declared	**1B-** **1-** Randomization Allocation concealment::

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	2 arms n=27 Italy	**Sex** m/f: 67/33% **CTX: Oxaliplatin based** (85mg/m^2) FOLFOX4 **,** every 2 weeks, 12 cycles max	Arm B: placebo? saline solution n=13		Grade 1: 0/13 Grade 2: 9/13 (69%) Grade 3: 4/13 (31%) (p=0.0037)	**cycles:** Arm A: 10.0 (5–12) Arm B: 9.2 (5–12)		method unclear Blinding: saline solution, observer blinding unclear ITT: no data Note: small sample size
Cascinu 2002 (Albers 2011)	RCT Single-center 2 arms n=52 Italy	**Colorectal cancer** **Age:** Arm A: 65 (40-77) Arm B: 65 (50-76) **Sex** m/f: 60/40% **CTX: Oxaliplatin based** (85mg/m^2) FOLFOX4 **,** every 2 weeks, up to 12 cycles max: 1,200	Arm A: **GSH** (1.5 mg/m^2) n=26 Arm B: placebo-saline solution n=26	***Patient assessments:*** NCI-CTCAE ***Neuro-physiologic assessments:*** Sural SNAP Conduction velocity Latency	**NCI-CTCAE:** **4 cycles** Arm A: Grade 1: 9/26 (35%) Grade 2: 1/26 (4%) Arm B: Grade 1: 6/26 (23%) Grade 2: 2/26 (8%) **8 cycles** Arm A: Grade 1: 7/21 (33%) Grade 2: 2/21 (9%) Arm B: Grade 1: 4/19 (21%) Grade 2: 6/19 (32%) Grade 3: 4/19 (21%) Grade 4: 1/19 (5%)	**Response rates:** **CR:** none **PR:** 7/26 (27%) vs. 6/26 (23%) **Median PFS**: 7 months in both groups	None reported.	**1B-** **1-** Randomization and allocation concealment: adequate Blinding: subject and observer yes ITT: yes

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		mg/m^2			**12 cycles** Grade 1: 6/10 (60%) Grade 2: 2/10 (20%) Grade 3: 1/10 (10%) Arm B: Grade 2: 2/8 (25%) Grade 3: 4/8 (50%) Grade 4: 2/8 (25%) **Sural SNAP:** Arm A: Baseline: 9.09±6.34µV 8 cycles: 8.71 ±5.50µV Arm B: Baseline: 10.98 ±6.92µV 8 cycles: 7.20 ±5.05µV			
Goshajinkigan (GJG)								
Nishioka 2011 Full text	RCT Single-center 2 arms n=55 Japan 01/07-12/09	**Colorectal Cancer** **Age:** Arm A: 67 (48-77) Arm B: 65 (52-80) **Sex** m/f: Arm A: 64/36% Arm B: 35/65% **CTX:**	Arm A: **GJG** 7.5 g/day in 2-3 doses during CTX orally n=22 Arm B: No treatment	**Primary endpoint:** Incidence of grade 3 CIPN **Secondary endpoints:** Percentage of grade 2-3 CIPN Base on Debiopharm Neurotoxicity criteria Tumor response AE (NCI-CTCAE)	**Grade ≥3 CIPN:** After 10 courses: Arm A: 0% Arm B: 12% After 20 courses: Arm A: 33% Arm B: 75% (p<0.01) No significant difference of grade 1/ 2 or worse CIPN. Data not shown. But percentage of CIPN lower in GJG in every course.	**CR:** Both 0% **PR:** Arm A: 12 (68%) Arm B: 13 (57%) Number of cycles: Arm A: 13 (4-32) Arm B: 12 (4-28)	Research Support Foundation, Grants in Aid Japan Society of Promotion of Science	**2B-** **1-** Randomization: yes, method unclear Blinding: no ITT: no Notes: Data missing

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		Oxaliplatin – based (85 mg/m^2) mFOLFOX 6	n=23 Calcium/ Magnesium infusion and other neuro-modulatory agents were forbidden		**Drop outs:** Arm A: 13 9 progressive disease 4 allergic reactions Arm B: 11 9 due to progressive disease One allergic reaction 1 greade 3 CIPn persisited No significant differences of AE between goups.	p=0.87 Cumulative dose: Arm A: 1105 (340-2720) Arm B: 1120 (340-2380) p=0.87		Small sample size No blinding
Kono 2009 Full text	RCT Multicenter 2 arms n=93 Japan 05/09-03/10	**Colorectal Cancer** **Age:** Arm A: 67 (40-88) Arm B: 61 (36-82) **Sex** m/f: Arm A: 52/48% Arm B: 56/44% **CTX:** **Oxaliplatin –** based (85 mg/m^2) FOLFOX 4 or m-FOLFOX6	Arm A: **GJG** 7.5 g daily For 26 weeks n=47 Arm B: placebo n=45 Mg/Ca infusions prohibited during first 26 weeks only	**Primary endpoint:** Incidence of grade 2 CIPN (NCI-CTCAE) **Secondary endpoints:** FACT-GOG-Ntx-12 score Time to CIPN Response Rates AE (NCI-CTCAE)	**CIPN until 8th course** (NCI-CTCAE): **Grade ≥2:** Arm A: 39% Arm B: 51% RR 0.76, 95%CI 0.47-1.21 **Grade 3:** Arm A: 7% Arm B: 13% RR 0.51, 95% CI 0.14-1.92 **Occurrence of CIPN:** Arm A: 5.5 (95% CI 4.1-not estimable) Arm B: 3.9 (95% CI 2.3-6.4) **FACT-GOG-Ntx 12:** After 26 weeks Arm A: 7.0 Arm B: 10.0 (p>0.5) No significant differences in AE	**CR:** Both 1 **PR:** Arm A: 14(51%) Arm B: 10(43%)	Epidemiological and Clinical research Information Network	**1B** **1+** Randomization: yes Blinding: yes ITT: yes Notes:

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Oxcarbazepine								
Argyriou 2006a (Albers 2011) Full text	RCT Single-centre 2 arms n=40 Greece	**Colon cancer** **Age:** Arm A: 61.8±9.1 Arm B: 65.8±6.9 **Sex** m/f: 50/50% **CTX: Oxaliplatin** (85mg/m^2), 12 courses	Arm A: **OXC** up to 600mg 2/day n=20 Arm B: no treatment n=20 (8 drop outs, 6 due to disease progression, 2 due to AE of OXC)	***Neuro-physiological assessments:*** Sural SNAP Superficial Peroneal SNAP Ulnar SNAP	**Neuropathy after 12 cycles:** 5/16 (31%) vs. 12/16 (75%), Risk Ratio : 0.42, 95%CI (0.19-0.91) (p=0.033), similar result in the ITT population (p=0.05) **CTX-discontinuation due to toxicity:** 2/20 vs. 0/20 **Sural SNAP** Mean Difference: 3.2 95%CI (-1.39-7.79) **Superficial Peroneal SNAP** Mean Difference: 1.8 95%CI (-1.18-4.78) **Ulnar SNAP** Mean Difference: 1.2 95%CI (-1.78-4.18)	No data for OS, PFS, DFS, TR.	Not reported.	**2B** **1-** Randomization: yes Allocation concealment: yes Note: small sample size ITT: yes
Lin 2006 (Albers 2011)	RCT Single-centre 2 arms n=14 China 12/02-12/04	**Colorectal cancer** (stage III) **Age:** Arm A: 58 (41–75) Arm B: 65 (43–78) **Sex:**m/f: 64/16% **CTX: oxaliplatin** (85mg/m^2)	**Acetyl-cysteine (NAC):** 1 RCT (*Lin 2006*) Arm A: NAC (1200 mg orally one and half an hour	***Patient assessment:*** NCI-CTC ***Neuro-physiological assessment:*** Sural SNAP Median CMAP	**Neurotoxicity** (NCI- CTC): Arm A/Arm B after 12 cycles of CTX: Grade 1: 3/5 (60)vs. 1/9 (11%) Grade 2: 1/5 (20%) vs. 5/9 (55%) Grade 3: 0 vs. 3/9 (33%) p= 0.01 Median follow-up: 18 month	No data for OS, PFS, DFS, TR.	Taiwan Cancer Foundation + Taipei Veterans General Hospital	**2B-** **1-** Randomization: yes (method unclear) Blinding: method unclear Note: very small sample

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		biweekly **+ 5FU (**425mg/m^2) weekly + leukovorine (20mg/m^2) weekly	before oxaliplatin) n=5 Arm B: Placebo n=9					size
Neurotropin								
Zhang 2012 Full text	RCT single-centre 2 arms n=80 China 05/10-05/11	**Colorectal cancer** (stage II + III) **Age:** Arm A: 55.1 Arm B: 57.3 **Sex** m/f: 66/34% **CTX:** Curative. Naive. **Oxaliplatin**-based (XELOX: 130 mg/m^2 + capecitabine; 8 cycles)	Arm A: **Neurotropin** (8 IU 2/day 14 days of 3 week cycle orally) n= 38 Arm B: No neurotropin n=41	***Patient assessments:*** NCI-CTC Oxaliplatin- specific scale (OSS)	**Neurotoxicity** NCI-CTC: ≥Grade 1: 38/38 (100%) vs. 41/41(100%) ≥Grade 2: 8/38 (21%) vs. 25/41 (61%) p=0.001 ≥Grade 3: 1/38 (2.7%) vs. 16/41 (39%) p<0.001 Oxaliplatin-specific neurotoxicity: ≥Grade 1: 38/38 (100%)vs. 41/41 (100%) ≥Grade 2: 5/38 (13%) vs. 21/41 (51%) p=0.001 ≥Grade 3: 0/38 vs.4/41 (10%) p=0.117 CTX-dose reduction due to neurotoxicity: 2/38 vs. 4/41, (p=0.743) Refusal of CTX due to neurotoxiciy: 2/38 (5%) vs.10/41 (24%), (p=0.04)	**Median number of cycles:** Arm A: no data Arm B: 5.2 No data for OS, PFS, DFS, TR.	Chinese Society of Clinical Oncology Research Funding	**2B** **1-** Randomization: yes Blinding: no ITT: no data

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Vitamine E								
Afonseca 2013 Full text	RCT single-center 2 arms n=34 Brazil 10/09-11/10	**Colorectal+ gastric cancer** **Age:** Arm A: 56 (29-76) Arm B: 57 (40-71) **Sex:** m/f: (53/47%) **CTX:** . **Oxaliplatin**-based regimens (FLOX, FOLFOX, EOX, XELOX) Both: Ca + Mg before + after oxaliplatin, zusätzlich zu Vitamin E	Arm A: **Vitamine E** (400mg daily) n= 18 Arm B: placebo n=16	***Patient assessments:*** NCI-CTC. Specific Gradiation Scale for oxaliplatin-induced neuropathy.	**Neurotoxicity** (NCI-CTC): Grade 1:12/18 (67%) vs.10/16 (63%) Grade 2: 3/18 (17%) vs.1/16 (6%), (p=0.45) Total: 15/18 (83%) vs.11/16 (68%)	No data for OS, PFS, DFS, TR.	Department of Hematology and Oncology, Faculdade de Medicina do ABC, Sao Paulo	**2B** **1-** Randomization yes Blinding: yes ITT: yes Notes: Very small size. Possible interaction of Mg/Ca + Vit E
Kottschade 2011 Full text	RCT Phase III Single-center 2 arms n= 207	Patients undergoing therapy with **neurotoxic CTX** Cancer: Breast,	Arm A: **Vitamine E** (300mg 2/daily orally)	**Primary outcome:** NCI- CTC **Secondary outcome:** Time to onset of	**Neurotoxicity** (NCI-CTC): Oxaliplatin only ≥Grade 2: 32% **Neurotoxicity** (NCI-CTC): Over-all ≥Grade 2:	No data for OS, PFS, DFS, TR.	North Central Cancer Treatment Group supported	**1B** **1+** Randomization yes Blinding: yes

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	USA 12/06-12/07	Lung or other **Age:** ≥50:61% ≤50: 39% **Sex** m/f: 18/82% **CTX:** Curative. Naïve. **Oxaliplatin** (26%), **Cisplatin**, **Carboplatin**, **Taxane** (58%)or combination	n= 96 Arm B: Placebo n= 93	grade 2+ sensory neuropathy (SN). Duration of SN. Dose reduction or omissions.	Arm A: 33/96 (34%, 95% CI 25-44.8) vs. 32/93 (29%, 95%CI 20.1-39.4), p=0.43 **Time to onset of ≥Grade 2 SN:** 58 days, 95%CI (43.0-97.0) vs. 69 days, 95%CI (49.0-105.0) p=0.58		by Public Health Service grants	ITT: yes Notes: inadequate dose of vit E
Venlafaxine								
Durand 2011	RCT Phase III Multicenter 2 arms France 10/05-05/08	**Patients under oxaliplatin treatment** With any kind of cancer **Age:** Arm A: 67.9 (32-82.7) Arm B: 67 (44.8-84.8) **Sex** m/f: 56/44%	Arm A: **Venlafaxine** 50 mg daily + venlafaxine extended release 37.5 mg on day 2-11 n=24 Arm B:	**Primary outcome:** Pain relief of 100% Assessed with Neuropathy Pain Symptom Inventory (NPSI) and NRS; **Secondary endpoints:** chronic neurotoxicity with OSS ≥50% pain relief AE	**Acute neuropathy:** Full pain relief: Arm A:31.3% Arm B: 5.3% (p= 0.03) **Chronic neuropathy:** Any grade: Arm A: 61.5% Arm B: 95.5% (p=0.06) Grade 3: Arm A: 0% Arm B: 33.3% (p=0.03)	**AE:** No grade 3-4 AE in arm A Grade 1-2 nausea, vomiting, somnolence and asthenia significantly more often in venlafaxine arm	EUREKA Sanofi Aventis France	**2B-** **1-** Randomization: yes Blinding: yes ITT: no data Notes: investigated acute neurotoxicity,

Referenz	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		CTX: Oxaliplatin Up to 100 mg/m^2	Placebo n=24					sample size insufficient

Carboplatin/Paclitaxel

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Acetyl-L-Carnitine								
Hershman 2013	RCT Multi-center 2 arms n=409 USA 09/09-	**Breast Cancer** **Age:** Arm A: 52 (27-80) Arm B: 50 (26-77) **Sex** m/f: 0/100% **CTX: Paclitaxel**	Arm A: **Acetyl-L-carnitine** (500mg daily for 24 weeks) n=208	**Primary outcome:** ***Quality of Life:*** FACT-Ntx: 11 items, higher scores reflect less neurotoxicity	**FACT-Ntx-Score** (fitted scores): 12 week: Arm A: 35.4 Arm B: 36.3 (p=0.17) 24 week: Arm A: 35.5 Arm B: 37.3 (p=0.01)	-no significant differences for adverse effects -no data for PFS, OS etc.	ALC by Thorne Research And Dawn L. Hershman	**1B** **1+** Randomization:y Blinding: yes ITT: no data

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	02/11	(at least 4 cycles) or **Docetaxel** (at least four cycles) –based regimes	Arm B: Placebo n=201	**Secondary outcome:** ***Patient assessment:*** NCI-CTC	**Neurotoxicity (NCI-CTC):** **Motor neuropathy** Arm A: Grade 1: 3/202 (1.5%) Grade 2: 4/202 (2%) Grade 3: 2/202 (1%) Grade 4-5: 0 Arm B: Grade 1: 5/194 (2.6%) Grade 2: 5/194 (2.6%) Grade 3-5: 0 (p=0.93) **Sensor neuropathy** Arm A: Grade 1: 57/202 (28%) Grade 2: 14/202 (7%) Grade 3: 5/194 (2.5%) Grade 4: 1/202 (0.5%) Arm B: Grade 1: 68/194 (35%) Grade 2: 13/194 (6.7%) Grade 3: 1/194 (0.5%) Grade 4-5: 0 (p=0.46)			
Amifostine								
Albers 2011 Including **Kanat**	**Sytstematic review** Including 2 RCTs	*Kanat 2003:* **Non-small cell lung cancer** n=38	Arm A: **Amifostine** (910 mg/m^2	**Clinical evaluation:** Clinical impairment. **Electro-physiologic evaluations:** SNAP	**Clinical impairment:** Paresthesias (grade 2): 8/19 (42%) vs. 18/19 (95%) Risk Reduction: 0.59 95%CI (0.36-0.98)	No data for OS, PFS, DFS, TR.	None reported.	**2B** **1-** Randomization: method unclear

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
2003 Lorusso 2003 Full text	for paclitaxel + carboplatin Search: Up to 08/10	**Age:** ≥18 **Sex:** Either sex. **CTX: Paclitaxel** (175mg/m^2) **Carboplatin** (AUC = 6).	every 3 weeks x 6) n=19 Arm B: No treatment n=19	**Functional activities of daily living**	**Functional activity of daily living:** decrease: 2/19 (11%) vs. 9/19 (47%) Risk Reduction: 0.22 95%CI (0.06-0.90) SNAP amplitudes showed no difference between the groups.			Blinding: no ITT: no data Notes: very small sample size
Albers 2011 Including Kanat 2003 **Lorusso 2003**		*Lorusso 2003:* **ovarian cancer** n=187 **Age:** ≥18 **Sex** m/f: 0/100% **CTX: Carboplatin+ Paclitaxel** (175 mg/m^2) for 6 cycles.	Arm A: **Amifostine** (910 mg/m^2) n=94 Arm B: No treatment n=93	Neurotoxicity evaluated by clinical examination but not further described.	**Neurotoxicity**: Grade 3-4: Arm A:19/508 evalutions (3.7%) Control: 37/514 evaluations (7.2%) (p = 0.02) Drop outs: Anaphylactic reaction to paclitaxel: 4 (2 each arm) disease progression: 16 patients	**Progression of disease:** 47 (55.9%) vs.43 (48.8%) p not significant	None reported.	**1A** **1++** Randomization: yes Blinding: no ITT: no data
De Vos 2005 Full text	RCT Phase II multi-center 2 arms n=90	**Ovarian cancer** **Age:** Arm A: 60 (35-77) Arm B: 59 (39-	Arm A: **Amifostine** (740 mg/m^2) n=45	**Toxicity Rating:** NCI-CTCAE **Quality of Life:** EORTC	**Neurotoxicity** (NCI-CTC) per cycles: Grade 1: 48% vs.45% Grade 2: 2% vs.12% Grade 3: 1% vs. 2% (p<0.001)	**Survival at 36 month:** Arm A: 70% Arm B: 52% No data for CI/p-value	Bristol-Myers Squibb Schering-Plough	**1B-** **1+** Randomization: Yes

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	Netherlands 07/1998-04/01	76) **Sex** m/f: 0/100% **CTX:** Curative or palliative. Naïve. **Paclitaxel** (175 mg/m^2) **Carboplatin** (AUC = 6). Up to 6 cycles.	Arm B: No treatment n=45	PFS OS	After 6 cycles: Arm A: Grade 1: 31/45 (69%) vs 25/45 (55%) Grade 2: 3/45 (7%) vs. 12/45 (27%) Grade 3: 3/45 (7%) vs. 2/45 (4%) (p=0.073) **QoL** (EORTC): Scores showed no difference between both arms. **Discontinuitation of paclitaxel:** Due to neurotoxicity: 3 (Arm B) **Drop outs:** 4 due to neurotoxicity 3 due to patient refusal	**Progression Free Survival:** Arm A: 22 months Arm B: 16 months (p=0.16) Follow up: 24 months **Number of cycles:** Arm A=254 Arm B= 251		Blinding: no ITT: yes
Hilpert 2005 Full text	RCT Phase II Single-center 2 arms n=72 Germany	**Ovarian cancer** **Age:** ≥18 **Sex** m/f: 0/100% **CTX:** Naïve. TC: **Paclitaxel** (175mg/m^2)+ **Carboplatin** (AUC=5) or TC + **Epirubicin** (6mg/m^2) (=TEC	Arm A: **Amifostine** (740 mg/m^2 prior to CTX) n=37 Arm B: Placebo n=34	**Primary outcome:** Vibration perception treshold (VPT) Vibration dis-appearance treshold (VDT) **Secondary outcome: Toxicity Rating:** NCI-CTCAE	**Neurotoxicity** (NCI-CTC) per cycle: Arm A vs. Arm B (%): Grade 0: 46 vs. 33% Grade 1: 40 vs. 49% Grade 2: 13 vs. 20% Grade 3: 1/0% (p=0.0103) **VPT Hands:** Arm A: 3.18 µm (5 cycles) Recovery after 6 month follow-up to baseline values. Arm B: 3.83 µm (6 cycles) VPT values remained pathologic	**Number of cycles:** Arm A: 203 over all Arm B: 187over all	Essex Pharma GmbH (maufacturer of amifostine)	**1B-** **1+** Randomization Yes, method unclear Blinding:yes ITT: no data

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
				Quality of Life: EORTC **Clinical evaluation:** Patella + achilles tendon reflex activities. 2-point discrimination Specific sensory symptoms (patient questionnaire incl. pain+sensory neuropathy)	(p=0.0114) **VPT Feet:** Arm A: 5.25 µm (6 cycles) Arm B: 11.88 µm (3 month follow-up) (p=0.0015) **VDT Hands:** Arm A: 2.75 (6 cycles) Arm B: 2.93 (3 cycles) (p=0.0038) **VDT Feet** (6 cycles): Arm A: 5.42 µm Arm B: 8.61 µm (p=0.0012) **Subjective assessments:** (questionnaires) No significant differences in incidences of sensory symptoms. **QoL** (EORTC): Amifostine failed to improve quality of life. No effect of amifostine on pain symptomatology, fine global motor activities, paraesthesia, prickle etc. Impairment of self-estimated skilfulness significantly more often in placebo group: Arm A/Arm B: 12/17 (p=0.04) **Other toxities:** Amifostine treated patients were significantly at a disadvantage with			

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
					regard to dyspnoea (p=0.0062), infection(P=0.0238), nausea (p=0.0005) and vomitting (p=0.0091).			
Leong 2003 Full text	RCT Single-center 2 arms n=60 Singapore 08/97-02/02	**Non-Small-Cell Lung Cancer, unresectable** **Age:** Arm A: 65 (40-77) Arm B: 65 (33-76) **Sex** m/f: 80/20% **CTX:** Curative. Naïve. Induction: **Paclitaxel** (175 mg/m^2)+ **Carboplatin** (AUC=6) **+RTX** (60-66 gy, 30 fractions + 60mg/m^2 paclitaxel)	Arm A: **Amifostine** (740 mg/m^{2,} , 2 dosages) n=30 Arm B: Placebo n=30	**Toxicity Rating:** NCI-CTCAE **Electro-physiologic measures:** Median, proximal + distal latency, nerve conduction velocity, F-wave latency a-SAP a-CMAP (ulnar, pereonal, tibial +sural) OS, MS, PFS	**Neurotoxicity** (NCI-CTCAE): Motor+sensory neuropathy: Grade 2-3: 5/ 21 (24%) vs. 10/27 (37%) (Diff.: -13%; 95%CI (-36%-13%)) Sensory neuropathy: Grade 1: 18/21 (86%) vs.18/27(67%) Grade 2: 1/21 (5%) vs. 6/27 (22%) Grade 3: 2/21 (10%) vs. 1/27(4%) Neurophysiologic parameters showed worsening in both arms but no significant difference . **Drop outs:** Patient refusal: 2 Early death: 6 Disease progression: 3 Unstable angina pectoris: 1	**Overall survival:** Hazard Ratio: 0.84 95%CI (0.46-1.52) (p=0.56) **Median OS:** 12.5 vs. 14.5 months **Median PFS:** 9.0 vs. 13.0 months, Hazard ratio: 0.81 95%CI (0.44-1.51) (p=0.50)	Schering Plough providing amifostine	**2B** **1-** Randomization yes Blinding:yes ITT: no data Notes: author: doses of amifostine might have ot been high enough High number of drop-outs
Gelmon 1999 Full text	RCT Phase II Multi-center	**Breast Cancer** **Age:** Arm A: 47 (32-	Arm A: **Amifostine** (910	**Toxicity Rating:** NCI-CTCAE **Clinical evaluation:**	**Neurotoxicity** (NCI-CTCAE): Grade 1: 13/20 (65%) vs. 9/20 (45%) Grade 2: 5/20 (25%) vs. 8/20 (40%) Grade 3: 2 /20 (10%) vs. 3/20 (15%)	No significant difference in tumor response rates	National Cancer Institute of Canada,	**2B** **1-** Randomization: yes

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	2 arms n=40 Canada	61) Arm B: 53 (33-75) **Sex** m/f: 0/100% **CTX:** Palliative. Naïve. **Paclitaxel** (initial 250mg/m^2 ,then 175mg/m^2)	mg/m^2 before CTX) n=20 Arm B: No treatment. n=20	VPT Patellar+ ankle reflexes, hand grip strength etc.	**Neurologic assessments:** No difference found in any oft he neurologic measures. **Other toxities:** Arm A/Arm B (%): Nausea : 90/55% (p=0.51) Vomiting: 75/40% (p=0.54)	between the groups. Response rate: 7/19 (36.8%) vs. 4/18 (22.2%)	Eli Lilly Co Canada, Bristol Myers, Squibb	Blinding: no ITT: no data Notes: Not blinded CI + p-values not always shown Small sample size
Goshajingkigan (GJG)								
Yoshida 2013 Journal of Oncology Full text	RCT Multi-center 2 arms n=29 Japan 03/07-03/09	**Ovarian/ Endometrial Cancer** **Age:** Arm A:55.6 Arm B: 59.7 **Sex** m/f: Arm A: 0/100% Arm B: 0/100% **CTX:** **Paclitaxel/Carboplatin –**based (Paclitaxel 175-180 mg/m^2 Carboplatin:	Arm A: **GJG** 7.5 g/ 3xday during CTX orally n=15 Arm B: No treatment n=14	**Primary endpoints:** NCI-CTCAE Fact-GoG Ntx Examination Current Perception Tresholds (CPT)	**Neurotoxicity (NCI-CTCAE):** After 6 weeks: Arm A: Grade 1: 9/15 (60%) Grade 2: 6/15 (40%) Grade 3: 0 Arm B: Grade 1: 6/14 (43%) Grade 2: 3/14 (21%) Grade 3: 2/14 (14%) No statistical differences In Fact-Gog-Ntx Arm A: 8.3±8.1 Arm B:5.5±.5 No statistical differences in CPT			

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		AUC 5-6) Max. 6 cycles						
Glutamate								
Loven 2009 Full text	RCT Multi-center 2 arms n=67 Israel	**Ovarian cancer** **Age:** Arm A: 59 (44-80) Arm B: 58 (35-79) **Sex** m/f: 0/100% **CTX:** **Paclitaxel** (175 mg/m^2, at least 6 cycles)+ **Carboplatin** (AUC=6)	Arm A: **Glutamate** (min. 500mg) n=23 Arm B: placebo n=20	**Toxicity Rating:** Severity Score (increment in grade of toxicity compared with baseline) for tingling, num-bness, pain, strength **Clinical evaluation:** Tactile, pain, vibratory perception **Electro-physiologic assessments:** Motor +sensory conduction velocity. Distal latency.	**Neurotoxicity** (Severity score): Sigificant benefit in the glutamate group for pain sensation, tingling and numbness. **Drop outs:** Progressive disease: 3 Severe skin rash: 2 Changed treating center: 1	No data for OS, PFS, DFS, TR.	Rotem Carmela Solgar Health products	**2B-** **1-** Randomization yes Blinding:yes ITT: no data Very small sample size, high drop-out rate (24/67)
Leal 2014 Full text	RCT Multi-center 2 arms n=185 USA 12/09-12/11	**Patients receiving Paclitaxel and Carboplatin treatments.** **Age:** Median 63 years (Arm A+B) **Sex** m/f: 19/81%	Arm A: **GSH** (1.5 mg/m^2) Arm B: placebo	***Quality Of Life:*** EORTC-QLQ-CIPN 20 ***Toxicity Rating:*** NCI-CTC	**Neurotoxicity** (NCI-CTC): Arm A: Grade≥2: 36/94 (38%) Grade≥3: 5/94 (5%) (p=0.45) Arm B: Grade≥2: 30/91 (33%) Grade≥3: 4/91 (4%) (p=0.77) EORTC-QLQ-CIPN 20:	**No interference of GSH with the antitumor activity of paclitaxel/carboplatin was detected.** Patients reaching 3rd cycle:	Public Health service grants, Grants by National Cancer Institute	**1 B-** **1-** Randomization: Yes Blinding:yes ITT: no data

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		CTX: **Paclitaxel** (80-200 mg/m^2) **Carboplatin** (AUC 5-7 every 21 or 28 days) for at least 12 weeks.			No significant differences for acute pain syndrome data or cumulative peripheral neurotoxicity.	Arm A: 75 Arm B: 71 6th cycle: Arm A: 64 Arm B: 58		
Omega-3-fatty-acids								
Ghoreishi 2012 Full text	RCT Single-center 2 arms n=69 Iran 04/10-10/11	**Breast Cancer** **Age:** Arm A: 46.19 ±9.76 Arm B: 45.70±12.0 **Sex** m/f: 0/100% **CTX:** **Paclitaxel** (175mg/m^2, 4 cycles)	Arm A: **Omega-3-fatty-acids** (640 mg, 3/day) n=30 Arm B: placebo n=27	**Primary outcome:** Reduced Total Neuropathy Score (rTNS): subjective and objective measures 0-28 points **Secondary outcome:** ***Electro-physiologic evaluations*:** Distal motor latency. a-CMAP Motor conduction velocity. a-SAP Sensory nerve conduction.	**Neurotoxicity** (rTNS): Arm A: Nomal: 21/30 (70%) vs. 11/27 (40%) Mild: 4/30 (13%) vs. 10/27 (37%) Moderate: 5/30 (17%) vs. 5/27 (19%) Severe: 0/30 (0%) vs. 1/27 (3.7%) Incidence: OR=0.3, 95%CI 0.10-0.88) p=0.029 Severity: p=0.054 **Nerve conduction measures:** Sensor nerve conduction: 13.33µv vs. 9.74 µv, (p=0.015) Other measure showed no significant differences. **Drop outs:** 4 due to critical health conditions 8 refusal of consent	No data for OS, PFS, DFS.	Dana Pharma Minami Nutrition	**2B** **1-** Randomization yes Blinding:yes ITT: no data Notes: Lack of longterm follow-up

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Davis 2005 Full text	RCT multicenter 3 arms n=117 Australia	Patients with solid tumors requiring CTX with paclitaxel and carboplatin **Age:** Arm A+Arm B: 58 (22-7 **Sex** m/f: 55/45% **CTX: Paclitaxel** (175mg/m2 + **Carboplatin** (AUC=6) 4-6 cycles	Arm A: **rhuLIF 2 µg/kg** day 0-6 n=36 Arm B: **rhuLIF 4 µg/kg** day 0-6 n=39 Arm C: placebo day 0-6 n=42	**Primary outcome:** Change of CIPN after 4 cycles with CPNE score (sum score out of ulnar, median, sural, peroneal NVC measures) drom 0-1 **Secondary outcome:** H- reflex latency VPT Symptom scores QoL with EORTC-CIPN 32 AE with NCI-CTCAE	**Change of CIPN:** no significant differences between groups after 4th and 6th cycle **Drop-outs:** Arm A: 36% Arm B: 33% Arm C :28% **AE (NCI-CTCAE):** Injection site reactions: Arm A: 28% Arm B: 36% Arm C: 5% ($p<0.05$) Erythema: Arm A: 11% Arm B: 23% Arm C: 5% Rigors: Arm A: 8% Arm B: 28% Arm C: 2% Vomiting: Arm A: 33% Arm B: 44% Arm C: 52% rhuLIF patients reported greater improvement in global health and less fatigue (no data reported) CPNE score was claimed to be sensitive and correlating with other	No data for OS, PFS, TR etc.	None reported	**2B** **1-** Randomization: yes, method unclear Blinding: yes ITT: yes Notes: High rate of drop- outs CI not shown information missing

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
					scores (no data reported)			
Vitamin E								
Argyriou 2005 Full text	RCT Single-center 2 arms n=40 Greece 03/03-03/04	**Patients receiving Paclitaxel or/and Cisplatin** **Age:** Arm A: 55.8±12.6 Arm B: 57.5±11.4 **Sex** m/f: 58/42% **CTX:** Naïve. **Cisplatin** and/or **Paclitaxel**. 6 courses.	Arm A: **Vitamin E** (300mg 2/day) n=20 Arm B: No treatment. n=20	**Clinical evaluation:** NSS, NDS **Electro-physiologic evaluations:** a-CMAP MCV,SCV Distal motor latancy F-wave,a-SAP **PNP score** summarizes clinical+electro-physiologic measures	**Neurotoxicity** (PNP-score): Grade 1: 1/16 (6%) vs. /15 (20%) Grade 2: 3/16 (19%) vs. 5/15 (33%) Grade 3: 0/16 (0%) vs. 3/15 (20%) (p=0.019) Drop outs. Death: 4 vs. 5 Disease progression: 2 vs. 3	No data for OS, PFS, DFS, TR.	Eviol, GA Pharma-ceutics, Athen	**2B** **1-** Randomization yes Blinding: no subject blinding ITT:yes Notes: very small sample size
Kottschade 2011 Full text	RCT Phase III Single-center 2 arms n= 207 USA 12/06-12/07	Patients undergoing therapy with **neurotoxic CTX** Cancer: Breast, Lung or other **Age:** ≥50: 61% ≤50: 39%	Arm A: **Vitamine E** ($300mg^2$/ daily orally) n= 96 Arm B:	**Primary outcome:** NCI- CTC **Secondary outcome:** Time to onset of grade 2+ sensory neuropathy (SN).	**Neurotoxicity** (NCI-CTC): Paclitaxel only ≥Grade 2: 58% **Neurotoxicity** (NCI-CTC): Over-all ≥Grade 2: Arm A: 33/96 (34%, 95% CI 25-44.8) vs. 32/93 (29%, 95%CI 20.1-39.4), p=0.43	No data for OS, PFS, DFS, TR.	North Central Cancer Treatment Group supported by Public Health Service	1B 1+ Randomization: y Blinding: y ITT: yes Notes: inadequate

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		Sex m/f: 18/82% **CTX:** Curative. Naïve. Oxaliplatin (26%), Cisplatin, Carboplatin, **Taxane** (58%)or combination	Placebo n= 93	Duration of SN. Dose reduction or omissions.	**Time to onset of ≥Grade 2 SN:** 58 days, 95%CI (43.0-97.0) vs. 69 days 95%CI (49.0-105.0) p=0.58		grants	dose of vit E No clear difference between CTX groups

Vinca-alkaloids

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Org 2766								
Koeppen 2004	RCT Multi-center	**Hodgkin and Non-Hodgkin-Lymphoma**	Arm A: **Org2766** (2mg s.c.	**Primary outcome:** Neuropathy-free interval	**Neurotoxicity:** Feeling of numbness: Essen: 86.1%	Response Rate: 61/73 (84%)	Organon International	**1B-1+**

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Full text	2 arms n=150 Germany / Netherlands 11/91-10/94	**Age:** Essen: Arm A: 42.9(18-68) Arm B: 41.5(19-79) Amsterdam: Arm A: 52 (18-76) Arm B: 52.4(20-76) **Sex** m/f: 62/28% **CTX:** Naïve. **Vincristine** (8-32mg) based schemes. CEBOPP-protocol (Essen) or scheme adapted to histologic diagnosis (Amsterdam)	before and after VCR) n=75 Arm B: Placebo n=75	**Secondary outcomes:** **Clinical evaluation:** 10-point score for neuropathic symptoms . Tendon reflex activities. VPT VDT **Quantitative evaluations:** Muscle strength. **Toxicity Rating:** **Quality of Life:** questionnaire for QoL	Amsterdam: 41.2% No signifiant difference between the study groups (p=0.17, p=0.13) No secondary endpoint showed statistically relevant differences between the study groups. .	vs. 64/74 (86%)		Randomization: yes Blinding: yes ITT: no, per -protocol Notes: missing effect measures for neurotoxocity

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Van Kooten 1992 Full text	RCT Single-center 2 arms n=30 Netherlands	**Hodgkin** (8) **and Non-Hodgkin-Lymphoma** (20) **Age:** Arm A: 44.7 Arm B: 54.7 **Sex** m/f: 61/39% **CTX:** Naïve. **Vincristine Sulfate** (max.2mg) based scheme	Arm A: **Org 2766** (s.c. Hodgkin: max.16mg NHL: 12mg) n=13 Arm B: Placebo n=15	**Clinical evaluation:** Questionnaire (Pain, parasthesia, numbness). Strength using Medical Research Scale. Sensory function. Tendon Reflex actvities. VPT. Thermal discrimination treshold.	**Neurotoxicity** Sensory complaints questionnaire: Total: 8/13 (62%) vs. 12/15 (80%), p>0.05 Numbness: 6/13 (46%) vs. 11/15 (73%), p<0.05 Neurologic signs: Paresis hand/foot muscles: 1/13 (8%) vs. 5/15 (33%) Sensory disturbance: 2/13 (15%) vs. 8/15 (53%), p<0.05 VPT showed no significant difference. (p=0.25)	**Complete Tumor Response:** Arm A: 9/13 (69%) Arm B: 7/15 (47%) No data for CI or p-value.	Organon International BV	**2B** **1-** Randomization: yes Blinding: yes ITT: yes Notes: median ages differ significantly Small sample size

Bortezomib

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Bortezomib s.c.								
Moreau 2011 Full text	RCT Phase III Multi-centre 2 arms n=222 France 07/08-02/10	**Multiple Myeloma** **Age:** Arm A: 64.5(42-88) Arm B: 64.5(38-86) **Sex** m/f: 55/45% **CTX:** Naïve. **Bortezomib** (1.3mg/m^2) up to 8 cycles	Arm A: **Sub-cutaneous Bortezomib** (1.3mg/m^2 s.c.) n=148 Arm B: **Intravenous Bortezomib** (1.3mg/m^2 i.v.) n=4	**Primary outcomes:** Overall Response Rate (ORR) Complete Response (CR) Partial Reponse (PR) after 4 cycles of Bortezomib only. **Secondary outcomes:** PFS, Time to response, duration of response, time to progression, local tolerability Adverse effects (NCI-CTC)	**Neurotoxicity** (NCI-CTC): Over all: 56/147 (38%) vs. 39/74 (53%) ≥Grade 2: 35/147 (24%) vs. 30/74 (41%) ≥Grade 3: 7/147 (5%) vs. 11/74 (15%), p<0.05 **Event rate o PNP-onset afte 2 cycles:** 5.8% vs. 18.8%	**Number of cycles:** Arm A: 8 (1-10) Arm B: 8 (1-10) **ORR** (after 4 cycles): Arm A: 61/145 (42%) vs. Arm B: 31/73 (42%) (p=0.002) **CR** (after 4 cycles): Arm A: 9/145 (6%) vs.Arm B: 6/74 (8%) (p=0.002)	Johnson& Johnson Pharma-ceutical Research and Developm ent, Millenium Pharma-ceutics	**1B-1+** Randomization yes Blinding: no ITT: yes Notes: sponsor had full access to all data, interpretation and writing of the report

Appendix 5: Tables of evidence for therapy of CIPN

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
Amitriptyline								
Kautio 2008 Full text	RCT Single-center 2 arms n=44 Finnland 01/02-08/04	**Patients who had received 2 month of neurotoxic CTX at least.** **Age:** Arm A: 52 (37-67) Arm B: 54 (35-67) **Sex** m/f: 27/73% **CTX: Neurotoxic CTX over at least two month duration.** Vinca alkaloids: 15/44 (34%) Platinum derivates: 14/44 (32%) Taxanes:	Arm A: **Amitriptyline** (10mg/d, up to 50mg) n=17 Arm B: placebo n=16	**Primary outcome:** ***Patient assessments:*** Improvement of neuropathic symptoms using 5-point verbal rating scale **VRS** (complete-moderate-some relief-no change-symptoms worse) **Secondary outcomes:** ***Patient assessments:*** NCI-CTC. Patient questionnaires of neuropathic symptoms (global improvement scale 1-10). EORTC Neuropathic Pain	**Verbal rating scale of relief:** Arm A: Complete relief: 2/17 (12%) vs.0/16 (0%) Major relief: 1/17 (6%) vs. 4/16 (25%) Some relief: 5/17 (29%) vs. 1/16 (6%) No change: 7/17 (41%) vs. 7/16 (44%) Worsening: 2/17 (12%) vs. 4/16 (25%) p>0.05 **Global improvement** (scale 1-10): Mean ±SD Arm A: 3.4 ±3.6 Arm B: 1.9± 3.1 (p>0.05) **Quality of Life:** Global Health Score (QLQ-C30): Improved in Arm A (p=0.038) but only temporary. Drop outs:	No data for OS, PFS, DFS, TR	Sources of support: None	**2B** **1-** Randomization yes Blinding: yes ITT: yes Notes: small sample size. Dose of amitriptyline might have been too low.

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		13 (30%) Combination: 2 (4%)		Symptom Inventory. Depression, Sleep	Adverse effects < 4 wks: 3 Neurotoxic chemotherapy ceased < 4 wks :4 Rejected from analyses because of non-compliance: 2			
Duloxetine								
Smith 2013 Full text	RCT Phase III multi-center 2 arms n=231 USA 04/08 - 03/11	**Patients with duration >3 month CTX induced peripheral neuropathy after completion of CTX.** **Age:** Arm A: 60 (30-≥70) Arm B: 59 (30-≥70) **Sex** m/f: 37/63% **CTX:** Paclitaxel, other taxane or oxaliplatin, other platinum	Cross-over design Arm A: D/P first **Duloxetine** (up to 60mg for 5 weeks), than placebo n=115 Arm B: P/D first Placebo than duloxetine n=116	**Primary outcome:** ***Patient assessments:*** Pain severity items (0-10 score) (BPI) **Seondary outcome:** ***Patient assessments:*** Brief Pain Inventory Short Form. QoL using FACT/GOG-Ntx. NCI-CTC	**Decrease of neuropathic pain** (BPI): 1.06 (95% CI, 0.72-1.40) vs. 0.34 (95% CI, 0.01-0.66) (P = 0.003) **Any decrease in pain:** Arm A: 59% Arm B: 38% **Relative Risk** of experiencing pain in Arm A compared to Arm B: 30% pain reduction: 1.96 95%CI (1.15-3.35) 50% pain reduction: 2.43 95%CI (1.11-5.30 Change in pain interference with daily function: Arm A: 7.9 95%CI (5.4-10.5) Arm B: 3.5 95%CI (1.1-5.9) **QoL** (FACT/GOG-Ntx) mean change:	No data for OS, PFS, DFS, TR.	NCI Division of Cancer Prevention. Eli Lilly providing study drug and placebo	**1B** **1+** Randomization yes Blinding: no ITT: yes

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
					Arm A: 2.44 95%CI (0.43-4.45) Arm B: 0.87 95%CI (1.09-2.82) Exploratory analyses results suggest that patients who received platinum compounds			
Gabapentine								
Rao 2007 Full text	RCT Phase III Single-center 2 arms n=115 USA 03/02-12/03	**Patients with duration >1 month CTX induced peripheral neuropathy** **Age:** Arm A: 59 (28-84) Arm B: 60 (25-80) **Sex** m/f: 27/73% **CTX: Neurotoxic CTX** active, discontinued or completed (Vinca alkaloids:	Cross over design: Arm A: G/P group: First: **Gabapentine** (300mg capsules up to 2700 mg a day) Second: placebo n=57 Arm B: P/G group	**Primary outcome:** ***Patient assessments:*** NRS (Numeric Rating scale pain 1-10) ECOG-NS: Eastern Cooperative Oncology Group neuropathy scale: 0=no, 1=mild, 2=moderate, 3=severe paresthesia, sensory loss, loss of tendon reflexes)	**Neurotoxicity**: ECOG-NS (14 weeks) Arm A/B: 1.5/1.5 (p=0.7) NRS 'worst pain' (14 weeks) Arm A/B: 4.2/3.2 (p=0.05) **Adverse events:** end of 6 weeks: GP: 44/57 (77%) vs. PG: 50/58 (86%), end of 14 weeks: GP: 29/41 (71%) vs. PG: 31/43 (72%) There were no significant differences in secondary endpoints. Drop outs: Patient refual (presumably because of perceived lack of activity) in 20% and in 29% of	No data for OS, PFS, DFS, TR	Source of funding: none reported	**1B** **1+** Randomization: yes Blinding:yes Notes: cross over design (2 weeks washout)

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
		11/115 (10%) Taxanes: 50/115 (44%) Platinum	First: Placebo Second: Gabapentine n=58					
Gel (Baclofen, Amitriptyline HCl, Ketamine)								
Barton 2010 Full text	RCT Single-center 2 arms n=208 USA 02/08-10/08	**Patients with duration >1 month CTX-induced peripheral neuropathy** **Age:** Arm A: 59.9 Arm B: 62.1 **Sex** m/f: 39/61%	Arm A: 1.31 g **Gel "BAK": 10mg Baclofen, 40 mg Amitriptyline HCl, 20 mg Ketamine** (2/day over 4 weeks	**Primary outcome:** ***Patient assessments:*** Change in sensor neuropathy subscale (European Organization for Research	**Change in sensory neuropathy** compared to baseline (EORTC-CIPN): Arm A: 8.1 ± 15.05 Arm B: 3.8 ± 15.52 (95%CI (-0.6-9.3); p=0.053) **Change in motor neuropathy** compared to baseline (EORTC-CIPN): Arm A: 7.1 ± 13.72 Arm B: 1.8 ± 14.05	No data for OS, PFS, DFS, TR	National Cancer Institute's CCOP program	**1B-1+** Randomization: yes Blinding:yes ITT: yes Notes: high number of drop-outs: 53/208 (25%)
Lamotrigine								
Rao 2008 Full text	RCT Single-center 2 arms n=131 USA 02/04-	**Patients with duration >1 month CTX-induced peripheral neuropathy**	Arm A: **Lamotrigine** (target: 300mg, start with 25mg, 10	**Primary outcome:** ***Patient assessments:*** NRS (Numeric Rating scale pain 1-10). ECOG-neuropathy	**Numeric Rating scale pain** decrease from baseline: Arm A: 0.3 Arm B: 0.5 (p=0.56) **ECOG-neuropathy scale:**	No data for OS, PFS, DFS.	Glaxo SmithKline provided study drug, no other funding	**1B-1+** Randomization: y Blinding:y ITT: no data

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	03/05	**Age:** Arm A: 62 (29-84) Arm B: 59 (34-82) **Sex** m/f: 41/59% **CTX: Neurotoxic CTX** Active or completed for at least 1 month CTX-induced neuropathy Vinca alkaloids: 44/125 (35%) Platinum compounds: 9/125 (7%) Taxanes: 34/125 (27%) Combination: 35/125 (28%)	weeks + than tapering off over 4 weeks) n=63 Arm B: placebo n=62	scale: 0=no, 1=mild, 2= moderate, 3=severe paresthesia, sensory loss, loss of tendon reflexes). **Secondary outcomes:** ***Patient assessments:*** Short Form-McGill Pain. Questionnaire. Brief Pain Inventory Short Form. Subjective Global Impression of Change. Symptom Distress Scale. Profile of Mood State. QoL.	Arm A: 0.4 Arm B: 0.3 (p=0.36) Discontinuation of study: 33% vs. 18% (p=0.06) 13 vs. 10 atient refusal 7 vs. 1 adverse event 9 vs. 5 other No other differences were noted between the groups using the secondary endpoints (i.e. BPI; McGill, QoL Uniscale)		sources	Missing effect measures and absolute numbers
Nortriptyline								
Hammack 2002 Full text	RCT Cross-over Single-	**Cisplatin CTX and at ≥1 month painful neuropathy**	Arm A: **Nortriptyline** First up	**Primary outcome:** Neuropathic pain with verbal descriptive scale	**After first period:** **VAS pain scale** (0-100): Arm A: -7.7 Arm B: -2.7	**Drop outs:** 6 due to toxicities (4 placebo	Public Health Grants	**2B** **1-** Randomization:

Reference	Type of study mono vs. multi-centre, arms, n=, period, country	Patient characteristics cancer, age, sex (m/f), CTX	Intervention: (supportive therapy.: Arm A) Controls (Arm B)	Outcomes	Neurotoxicity	Survival Rates, Drop outs, Response Rates	Financing	Level of evidence (CEBM levels/ SIGN) Reasons for down-grading
	center 2 arms n=57 USA 02/95-01/96	**Age:** Arm A: 59.5 Arm B: 63.0 **Sex:** no data **CTX: Cispaltin** ongoing or terminated. Stratified to <300 mg/m^2 300-400 mg/m^2 >300 mg/m^2	to 100mg n=26 Arm B: Placebo first n=25	(VDS) Activities of daily life affected by neuropathy with VDS **Secondary outcome:** Neuropathic pain with visual analogue scale (VAS) descriptive Quality of Life with VAS Satisfaction scale from 0-4 AE	(p=0.78) Before cross-over insignificant, after cross-over significant (p=0.02) **Paraestehsia** (0-100): Arm A: 49 Arm B: 55 (p=0.78) **Pain effects daily life:** Arm A: 0.3 Arm B: 0.2 (p=0.04) **QoL:** Arm A: 4.6 Arm B: 7.7 (p=0.74) **After cross-over:** ≥10 point pain reduction: Arm A: 15/51 (29%) Arm B: 10/51 (20%) (p=0.04) No change in paraesthesia.	phase, 2 nortriptyline) **AE:** Dry mouth: Arm A: 62% Arm B: 31% (p=0.002) Dizziness: Arm A: 49% Arm B: 15% (P=0.002) Constipation: Arm A: 41% Arm B: 22% (p=0.07) Total number of AE in nortiptyline phase higher but no significant difference in desation, nausea, urinary hesitancy or other.		yes Blinding: yes ITT: yes Notes: Cross-over design Carry-over effect possible

Statement of authorship

I hereby declare, that I have written this thesis without any help from others and without the use of documents and aids other than those stated above. I have mentioned all used sources and cited them correctly according to established academic citation rules.

I assure that I did not use the aid of any commercial promotion advisors. I did not pay anyone for any service according to this dissertation thesis.

Halle (Saale), 20/03/2017 Juliane Beckmann

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Ich erkläre hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quelle gekennzeichnet.

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Halle (Saale), den 20.03.2017 Juliane Beckmann

Declaration of earlier attempts of dissertation

Hereby I declare that I have not completed or initiated a doctorate procedure at any other university

This dissertation work was not presented to an authority, neither inland or in other countries.

Halle (Saale), 20/03/2017 Juliane Beckmann

Erklärung über frühere Promotionsversuche

Hiermit erkläre ich, Ich erkläre, dass ich mich an keiner anderen Hochschule einem Promotionsverfahren unterzogen bzw. eine Promotion begonnen habe.

Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Halle (Saale), den 20.03.2017 Juliane Beckmann

Curriculum vitae

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Career:

January 2017- now	Assistant at the hospital "Martha Maria Dölau", Clinic of Anaesthesiology, Medical Director: PD Dr. med. Fritz
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School education:

1994-1998	Elementary school Kröllwitz in Halle
1998-2000	Secondary school Wittekind/Kröllwitz in Halle
2000-2007	Highschool Thomas-Müntzer Gymnasium Halle

University education:

October 2008-July 2015	Study of medicine at the Martin-Luther Universität Halle
March 2011	1. 1st State examination: Physikum
April 2014 to June 2015	2. 2nd State examination
March 2013	Dissertation in the Clinic for Haematology and Oncology/Institute for Medical Epidemiology, Biometry und Informatics of the Medical Faculty of the Martin-Luther-Universität Halle-Wittenberg Supervisors: apl. Prof. Dr. med. Karin Jordan Prof Dr. rer. nat. Johannes Haerting

Internships:

August 2011	Rehabilitation clinic for Oncology in Ahrenshoop
February/March 2012	Nephrology of the university hospital Halle
August 2012	Centre of renal transplantation university hospital Halle
February/March 2013	Clinic für Oncology and Haematology university hospital Halle
August 2013	Doctor's surgery for Oncology in Greifswald

Elective:

May – June 2014	Emergency department university hospital Halle
June- September 2014	Clinic für Oncology and Haematology university hospital Halle
September- December 2014	Clinic für Anaesthesiology und Intensive Care university hospital Halle
January- April 2015	Department of Surgery HELIOS Klinik Eisleben

Curriculum vitae

Extracurricular Engagement:

June 2010, 2011 & 2012	Organisation of theTeddybear-Hospital MLU Halle
August 2013	Active participation for an image film at the centre of medical simulation MLUHalle

Foreign experiences and languages:

2004/2005	Exchange student in Texas/USA Allen Highschool
2007/2008	Work and Travel in Australia
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Other qualifications

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Halle, 20/03/2017 Juliane Beckmann

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