Chemotherapy-induced neuropathy: prevention and treatment

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications:


ABBREVIATIONS

ADL = activities of daily living
CIPN = chemotherapy induced peripheral neuropathy
DNA = deoxyribonucleic acid
DRG = dorsal root ganglion
ECOG = Eastern Cooperative Oncology Group
EMA = European Medicines Agency
EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer item 30 of the quality of life questionnaire
FDA = the United States Food and Drug Administration
Ca = calcium
Mg = magnesium
HIV = human immunodeficiency virus
IENF = intraepidermal nerve fiber
NCI-CTC = the National Cancer Institute – Common Toxicity Criteria
NRS = Numerical rating scale
PGP 9.5 = protein-gene-product 9.5
PHN = postherpetic neuralgia
q3w = every three week treatment schedule
QoL = quality of life
QST = quantitative sensory testing
SNRI = serotonin-noradrenalin reuptake inhibitor
TCAs = tricyclic antidepressants
TNF-α = tumor necrosis factor alfa
TNS = Total Neuropathy Score
TRPA1 = Transient Receptor Potential Ankyrin 1
TRPM8 = Transient Receptor Potential Melastatin 8
TRPV1 = Transient Receptor Potential Vanilloid 1
VAS = Visual Analogue Scale
VRS = Verbal rating scale
ABSTRACT

Aims

The present study aimed to investigate the effect of amitriptyline in prevention (study III) and treatment (study II) of chemotherapy-induced peripheral neuropathy (CIPN). The secondary aims were to evaluate the prevalence and discomfort of CIPN in a clinical cohort predisposed to neurotoxic chemotherapy agents (study I), grading of neurotoxicity (study IV) and the changes in intraepidermal nerve fiber (IENF) density during the neurotoxicity treatment (study V).

Patients

The study included three cancer patient populations treated with neurotoxic chemotherapy at Helsinki University Hospital, Department of Oncology (studies I-IV) or Gynecology (study III) and Tampere University Hospital, Department of Oncology (study V). The first study population was screened between January 2002 and June 2004 from 448 patients aged 20 to 70 years, of whom 152 had neuropathic symptoms and were hence eligible for evaluation of the burden of neuropathic symptoms (I). Of those 152 symptomatic patients 33 patients had sensory neuropathic symptoms (numbness, tingling or pain) of at least moderate severity and were randomised to treatment study (II). Between February 2003 and May 2006 104 patients without previous neuropathy who started neurotoxic chemotherapy were randomized to the prevention study (III). Two different neurotoxicity scales were used with this population (IV). The fifth study consisted of 12 patients aged from 18 to 70 years starting adjuvant chemotherapy with taxanes or platinum derivatives (V).

Methods

In the first study (I) a questionnaire of chemotherapy adverse effects and neuropathy symptoms was used for screening. The intensity of the neuropathic symptoms was assessed with a Visual Analogue Scale (VAS) (I-III, V). During the clinical visits the patients were evaluated with physical examination including neurological status (I-III, V). Neuropathy
was scored according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) and Oxaliplatin Scales (II-V), and quality of life (QoL) with the European Organization for Research and Treatment of Cancer item 30 of the quality of life questionnaire (EORTC QLQ-C30) for cancer patients (II, III, V). The patients graded neuropathic symptoms by VAS in a diary twice a week during the whole study period (II-III). The skin biopsies (diameter 3 mm) were taken from the right distal leg 10 cm above the lateral malleolus at every study visit. Specimens were fixed in 10% formalin and then embedded in paraffin. Ten-um sections were immunostained with anti-protein-gene-product 9.5 (PGP 9.5) antibodies. The IENF count was determined with a light microscope at 400 x magnification blinded to the clinical status of the patient. Two adjacent skin sections were analyzed to get a proper estimation of the IENF count. For the estimation of epidermal area the point-counting was performed using square lattice. The normal value for IENF density was determined to be above 40 fibres per mm².

Results

Fifty-nine % of the screened patients reported neuropathic symptoms. Tingling (71 %), numbness (58 %) impaired sensory function (46 %) and pain in hands and feet (40 %) were the most common symptoms. The median intensity of neuropathic symptoms was 28/100 on VAS. Neuropathic symptoms were the third most commonly reported adverse effect symptoms. Every third patient (37 %) with neuropathic symptoms ranked them as the most troublesome symptom.

Comparing the NCI-CTC sensory and Oxaliplatin Scales the progression of the toxicity from mild (grade 1 or 2) to moderate or severe (grade 3 or 4) was detected more frequently with the Oxaliplatin scale. Of the patients with grade 3 or 4 toxicity with Oxaliplatin Scale 23/53 had grade 1 toxicity by the NCI-CTC scale, 18/53 had grade 2 and 12/53 had grade 3 neurotoxicity. The Oxaliplatin Scale was in line with the NCI-CTC scale in 12/53 patients with grade 3 symptoms.

No significant differences were found between the amitriptyline and placebo groups in the intensity of the neuropathic symptoms either in the treatment study or in the prevention study during the follow-up. In the prevention study sensory neuropathy was seen after 3, 6 and 9 chemotherapy cycles in 61 %, 57 % and 76 % of the patients, respectively. Amitriptyline improved statistically significantly quality of life (QoL) measured with the EORTC QLQ-C30 compared with placebo.
Reduced IENF density was found in 8/12 patients at baseline. During the follow-up IENF density increased significantly in six of them and remained unchanged in two. In four patients IENF density was normal both at baseline and at the end of follow-up period. Nine patients had neuropathic symptoms, but no association was found between neuropathic symptoms and IENF count.

**Conclusion**

CIPN is a common, albeit of mild intensity, adverse effect of neurotoxic regimens. There is no standard global method for assessment of CIPN. No prevention or treatment of CIPN exists except limitation of total dose or changing the treatment to a less neurotoxic agent. IENF density can be markedly reduced in some cancer patients even prior chemotherapy, which might partly influence the development of abnormalities in sensation and neuropathic pain.

**INTRODUCTION**

The first case report of sensory neuropathy secondary to chemotherapy agent cisplatin was published over 30 years ago (Kedar *et al.*, 1978). Nowadays, CIPN is a well recognized adverse event, and the awareness of its significance is increasing as neurotoxic drugs are used more frequently in adjuvant settings with more patients being cured. Survival benefit of adjuvant chemotherapy has been demonstrated at least in breast, ovarian, colorectal, lung, pancreatic and ventricular cancer and sarcomas. In addition, chemotherapy of testicular cancer and lymphomas is mainly curative. Life expectancy has prolonged also for patients with advanced cancer due to better treatment options, including multiple chemotherapy regimens. In advanced cancer, chemotherapy prolongs overall and progression-free survival and improves QoL, by reducing and preventing cancer-related symptoms.

The most neurotoxic chemotherapeutic agents are vinca-alkaloids, platinum derivatives and taxanes (Ocean and Vahdat, 2004; Quasthoff and Hartung, 2002). The incidence of neurotoxicity varies between the different chemotherapy agents. It appears in a dose-dependent manner and is usually highest when neurotoxic agents are used in combination. However, the mechanisms of CIPN are not fully understood.
Incidence of CIPN varies widely depending on cytotoxic agent, treatment schedule (total dose, dose intensity), combinations of different cytotoxic agents and patient population. Especially elderly population and patients with a pre-existing disorder of the peripheral nervous system (e.g. neuropathy associated with diabetes, malnutrition, alcoholism or inherited neuropathy) are at higher risk of developing severe and irreversible chemotherapy-induced neuropathy (Ocean and Vahdat, 2004). In the US, 50 % of all malignancies occur in persons aged 65-95 years. With increasing cancer incidence in the older population, it is expected that 60 % of all cancers will be detected in elderly patients in the next two decades (Balducci and Extermann, 2000).

CIPN is an important adverse effect as it may cause dose reductions or discontinuation of the anticancer treatment, which may deteriorate the prognosis of the patient. In the majority of the patients CIPN is reversible if recognized early enough and the treatment is discontinued or the dose is reduced. However, recovery may take months or even years. Chronic CIPN symptoms reduce significantly physical functioning and QoL of cancer patients. The typical clinical presentation of peripheral neuropathy is symmetric sensory and motor impairment in a length-dependent manner (distal extremities first), which causes paresthesia, numbness, pain and peripheral motor dysfunction.

Interest in CIPN has increased in the last years, including epidemiology, mechanisms, clinical burden, prevention and treatment of it. A possibility to either prevent or treat CIPN could thus affect not only physical functioning and QoL of the patients, but it could also indirectly improve survival.

With this study we aimed at investigating the prevalence and discomfort of neuropathic symptoms in relation to other toxicities of chemotherapy, and the possible effect of amitriptyline in prevention and treatment of neuropathic symptoms. In addition, we wanted to compare two different scales in grading of chemotherapy-induced neurotoxicity and do a pilot study of the changes of intraepidermal nerve fiber density during neurotoxic chemotherapy.
REVIEW OF THE LITERATURE

Anatomy of peripheral nervous system

The peripheral nervous system refers to parts of the nervous system outside the brain and spinal cord. It includes the cranial nerves and spinal nerves from their origin to their end.

The anterior horn cells motor neurons are located in the gray matter of the spinal cord and thus are anatomically part of the central nervous system although functionally they belong to the peripheral nervous system. In contrast to the motor system, the cell bodies of the afferent sensory fibers lie outside the spinal cord, in dorsal root ganglia.

Nerve fibers outside the spinal cord join to form anterior (ventral) motor roots and posterior (dorsal) sensory nerve roots (Figure 1). The ventral and dorsal roots combine to form a spinal nerve. Thirty of the 31 pairs of spinal nerves have dorsal and ventral roots.

Because sensory and motor cell bodies are in different locations, a nerve cell body disorder typically affects either the sensory or motor component but rarely both. Motor neuron dysfunction results in muscle weakness or paralysis. Sensory neuron dysfunction results in abnormal or lost se

Figure 1. A horizontal section of the spinal cord, and dorsal and ventral roots and a spinal nerve. (adopted from http://www.dartmouth.edu/~humana/atomy/figures/chapter_3/3-2.HTM )
A peripheral nerve trunk is comprised of axons of multiple neurons bundled in connective tissue fascicles surrounded by perineurium. The primary afferent axons are classified according to their diameter and conduction velocity (Table 1, Figure 2).

Table 1. Classification of the primary afferent axons according to their diameter and conduction velocity (adopted from http://thebrain.mcgill.ca)

<table>
<thead>
<tr>
<th>Type of nerve fiber</th>
<th>Information carried</th>
<th>Myelin sheath</th>
<th>Diameter (micrometerers)</th>
<th>Conduction speed (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-alpha</td>
<td>proprioception</td>
<td>myelinated</td>
<td>13 - 20</td>
<td>80 - 120</td>
</tr>
<tr>
<td>A-beta</td>
<td>touch</td>
<td>myelinated</td>
<td>6 - 12</td>
<td>35 - 90</td>
</tr>
<tr>
<td>A-delta</td>
<td>pain (mechanical and thermal)</td>
<td>myelinated</td>
<td>1-5</td>
<td>5-40</td>
</tr>
<tr>
<td>C</td>
<td>pain (mechanical, thermal and chemical)</td>
<td>nonmyelinated</td>
<td>0.2 – 1.5</td>
<td>0.5 - 2</td>
</tr>
</tbody>
</table>

Figure 2. Primary afferent axons (adopted from http://www.cidpusa.org/nerves.htm)

A-alpha fibers are the largest peripheral fibers, functioning as alpha-motoneurons and proprioceptive sensory fibers. A-beta fibers transfer tactile stimuli, whereas small fibers (including thinly myelinated A-delta fibers and unmyelinated C fibers) transfer mechanical pain and thermal stimuli.
**Disorders of the peripheral nervous system**

*Peripheral neuropathy* is a general term that indicates any disorder of the peripheral nervous system. The term *mononeuropathy* implies a focal lesion of a single peripheral nerve. *Mononeuropathy multiplex* describes the involvement of multiple separate noncontiguous peripheral nerves either simultaneously or serially. *Polyneuropathy* refers to simultaneous malfunction of many nerves throughout the body. Polyneuropathies can be classified in different ways, such as by cause, hereditary or not, or by part of which the nerve cell is mainly affected: the myelin sheath (*myelinopathy* or *demyelinating polyneuropathy*), the axon (*distal axonopathy*), or the cell body (*neuronopathy*). (England and Asbury, 2004)

Demyelinating polyneuropathy (due to loss of myelin or Schwann cells) affects mainly heavily myelinated fibers slowing nerve conduction and causing large-fiber sensory dysfunction (buzzing and tingling sensations), motor weakness and diminished reflexes. It can be divided to acquired or genetic: acute inflammatory demyelinating (polyradiculitis like Guillain-Barré syndrome) and chronic inflammatory demyelinating polyneuropathy or genetic metabolic disorders (e.g., leukodystrophy). Typical demyelinating polyneuropathy is severe motor weakness with minimal atrophy. (England and Asbury, 2004; Hughes, 2008)

Axonal polyneuropathy is the most common type of polyneuropathy. It is caused by damage to the axon transport system for cellular constituents, especially microtubules and microfilaments, leading to significant axon dysfunction. Axonal polyneuropathies can be divided according to the type of axon affected: small-fiber, (e.g., Fabry’s disease), large-fiber or both (England and Asbury, 2004). The smaller fibers at the most distal part of the nerve are first affected, because they have greater metabolic requirements. Thereafter the axonal degeneration ascends slowly producing the characteristic distal-to-proximal pattern of symptoms (stocking-glove sensory loss and weakness). Distal axonopathy is the most common response of neurones to metabolic or toxic disturbances. The most common metabolic causes are diabetes, renal failure, and hypothyreosis. A typical example of nutritional cause is vitamin B$_{12}$ deficiency. The most common toxic causes for axonal neuropathy are alcohol and neurotoxic drugs (England and Asbury 2004; Hughes, 2008). Central hypothesis is that dysfunctional mitochondria in distal axons are a common mechanism to explain length-dependency of peripheral neuropathies (Lehmann, 2011).

Many polyneuropathies have both motor and sensory involvement and some cause also dysfunction of the autonomic nervous system. There is some variation in clinical picture of peripheral neuropathies from different etiologies. Also peripheral neuropathy from a single etiology may manifest differently in different patients. The most common symptoms of
Peripheral neuropathy are sensory disturbances, including both the negative symptoms of numbness and sensory loss and the positive symptoms of pain and paresthesias. The sensory symptoms most often start in the distal extremities in a ‘glove-and-stocking’ distribution. Motor symptoms manifest as distal weakness and muscle atrophy. Deep tendon reflexes diminish. In addition, autonomic symptoms may occur which can include orthostatic hypotension or other cardiovascular disturbancies, erectile dysfunction or gastrointestinal disturbances. (England and Asbury, 2004)

If the cause of polyneuropathy is removed, regeneration is possible, though the prognosis depends on the duration and severity of the cause. (England and Asbury, 2004; Hughes, 2008)

**Neuropathic pain**

Neuropathic pain is a consequence of a lesion or disease affecting the somatosensory system (Jensen et al, 2011). Inflammatory or nociceptive pain is caused by tissue damage or potentially tissue damaging stimuli, whereas neuropathic pain is produced either by damage to, or pathological change in the system that normally signals pain. Painful symptoms arising in an area of altered sensation (hyposensitivity, i.e., impaired sensory function, or hypersensitivity, i.e., increased sensation to stimuli) refer to neuropathic pain. Neuropathic pain disorders are divided into central or peripheral neuropathic pain conditions on the basis of the site of the lesion. Basic characteristics of neuropathic pain are spontaneous pain (pain arising without stimulus) or abnormal response to non-painful or painful stimuli. Patients may report dysaesthesias (unpleasant and strange sensations in the skin, such as tingling and pins and needles), deep seated gnawing pain, abnormal thermal sensations (burning or ice cold) and less frequently shooting, stabbing, or electric shocks. Features of neuropathic pain may come out within days of nerve damage or can take months to develop. (England and Asbury, 2004; Hughes, 2008)

Symptomatic treatment of neuropathic pain is based on modulatory effect of the drug to the abnormal functioning sensory system. Recent evidence-based guidelines, based on randomized controlled trials, recommend topical lidocaine in peripheral neuropathic pain with a limited area of allodynia (e.g., postherpetic neuralgia (PHN), tricyclic antidepressants (TCAs), gabapentinoids (gabapentin and pregabalin) and serotonin-noradrenalin reuptake inhibitor (SNRI) drugs (duloxetine and venlafaxine) as the first line choices for neuropathic pain (Attal et al, 2010, Dworkin et al, 2007). Carbamazepine and oxcarbazepine are drugs of choice for trigeminal neuralgia. When the first line drugs fail to provide acceptable pain
relief for NP other than trigeminal neuralgia, tramadol and strong opioids (e.g., morphine or oxycodone) are recommended, providing the patient has no contraindications for opioid use. (Attal et al, 2010). The registration trials have used mainly two clinical conditions, (PHN) and painful diabetic neuropathy, but other neuropathic pain conditions are far less studied. Some neuropathic pain conditions, like painful HIV-related neuropathy or painful radiculopathy are more refractory to treatment than PHN and painful diabetic neuropathy. (Attal et al, 2010). Recently a new treatment, 8 % capsaicin plaster, has been approved by European Medicines Agency (EMA) for the treatment of peripheral neuropathic pain in non-diabetic adults (Astellas, 2011). It is used as a single application every 3 months. Capsaicin is a highly selective agonist for the transient receptor potential channel Vanilloid-Receptor Type 1 (TRPV1), located in nociceptors. Capsaicin causes initially TRPV1 activation (experienced as burning pain), and in some days ‘defunctionalisation’ of TRPV1, leading to pain reduction. It also results in reversible reduction in IENF density. (Anand and Bley, 2011). Capsaicin patch has shown efficacy in patients with PHN (Backonja et al, 2008) and painful HIV-related neuropathy (Simpson et al, 2008).

There is little evidence of the possibilities to prevent neuropathic pain. According to one small study, risk of PHN can be reduced with low-dose amitriptyline (25 mg) used for 3 months after acute phase (Bowsher, 1997). Prevention of herpes zoster with a vaccine naturally prevents PHN (Oxman et al, 2005). Risk of postsurgical neuropathic pain can be reduced by applying surgical techniques that avoid nerve damage (Kehlet et al, 2006). Optimizing glucose balance and controlling risk factors of atherosclerosis reduce the risk of painful diabetic neuropathy (Tesfaye et al, 2005). Avoiding predisposition to neurotoxic agents reduces the risk of painful toxic neuropathy.

**Peripheral neuropathies related to malignancies**

In a single cancer patient neuropathy with or without pain may be caused by the tumour, treatment or immunological mechanisms. The most common reason for cancer-associated neuropathy is infiltration or compression of a nervous structure by the tumour. Main anticancer treatments, i.e., surgery, radiotherapy and chemotherapy can cause peripheral nerve damage. Postsurgical neuropathic pain is not an uncommon phenomenon in a cancer patient, e.g., postmastectomy pain is thought to be consequence of 4-6 % of surgical procedures for breast cancer (Stevens et al, 1995). The development of radiotherapy
techniques has decreased the incidence of post-radiotherapy neuropathy, which may be acute or delayed (presenting after years) (Schierle and Vinograd, 2004).

The Paraneoplastic Neurological Syndrome Euronetwork and the European Federation of Neurological Societies have summarized the data acquired over the past 8 years on paraneoplastic syndromes, including those affecting the peripheral nervous system (Koike et al, 2011). Several types of neuropathies have been reported as paraneoplastic. Subacute sensory neuronopathy is a classical paraneoplastic neurological syndrome. It occurs mostly in small cell lung cancer (70–80 % of cases) and sometimes in breast or ovarian cancer, Hodgkin’s disease or sarcomas. The most usual symptoms are pain and paraesthesiae. Sensory loss may occur in the face, chest or abdomen, and in deep sensation it leads to severe sensory ataxia. Neuropathy often precedes the discovery of cancer, and the main treatment aims at obtaining oncological remission, which remains the best way to stabilize the neuropathy. (Behin et al, 2008)

Neuropathies related to lymphomas are quite rare and heterogeneous. They are associated with myelin associated glycoprotein IgM production. Myelin associated glycoprotein is a type I membrane protein and member of the immunoglobulin superfamily. It is supposed to be involved in the process of myelination by binding glycoconjugates and mediates certain myelin-neuron cell-cell interactions. The most aggressive high-grade B-cell lymphomas usually cause proximal infiltration and no demyelinating polyneuropathy, while Hodgkin’s lymphoma is associated with no demyelinating polyneuropathy (Behin et al, 2008).

Multiple myeloma itself can cause neuropathy. Therefore, a large proportion of patients who are started with cancer treatment for multiple myeloma already have neuropathy from their underlying malignancy or amyloidosis associated to it. For example 81-83 % of bortezomib-treated multiple myeloma patients had neuropathy before the treatment. Those having neuropathy prior to neurotoxic chemotherapy develop more severe neuropathy than those without preceding neuropathy, but the incidence of neuropathy is not increased (Richardson et al, 2006; Plasmati et al, 2007; Kaley and Deangelis, 2009).
Incidence of CIPN varies widely in the literature depending on the study. Approximately 30-40% of patients treated with neurotoxic chemotherapeutic agents develop peripheral neurotoxicity, being highest with cisplatin, paclitaxel, docetaxel, vincristine, oxaliplatin and bortezomib (Velasco and Bruna, 2010).

Neurotoxic agent, cumulative dose, dose intensity, duration of therapy, and coadministration of other neurotoxic chemotherapy agents affect to incidence of CIPN (Velasco and Bruna, 2009). In addition, patient related factors such as age, excessive alcohol consumption and pre-existing co-morbidities predisposing to neuropathy (e.g., diabetes, vitamin B12 deficiency, or hypothyroidism) increase the risk of CIPN. Patients with previous neuropathy are at risk to have progression of neuropathy when treated with neurotoxic chemotherapy (Chaudry et al, 2003). This may necessitate the selection of an alternative (less neurotoxic) chemotherapeutic agent. (Argyriou et al, 2011; Cavaletti, 2009; Kaley and Deangelis, 2009; Pachman et al, 2011)

Incidence of CIPN in daily practice may be even higher than incidence reported in clinical trials as patients in trials are highly selected. Especially elderly patients and patients with comorbidities are underrepresented in the studies. It has also been proposed that CIPN is underreported by the patients and underrecognised by the doctors (Velasco and Bruna, 2010).

While symptoms recover completely in the majority of the patients, in some cases CIPN is only partly reversible (Bakitas 2007). Peripheral neuropathy can impair patient’s physical functioning, activities of daily living (ADL) and QoL (Almadrones et al, 2004; Bakitas, 2007).

Patients who have neuropathy in the upper extremities experience different functional limitations compared to patients with neuropathy in the lower extremities (Bakitas, 2007). The former may experience difficulty in tasks demanding fine motoric skills such as buttoning buttons, zipping zippers, writing or sewing, whereas the latter, especially with advanced neuropathy can have difficulties in walking, climbing stairs, using car pedals and any activity which requires good control of balance. Elderly patients may become unable to live independently because the symptoms can lead to need of assistance in ADL. Depending on patients’ work, the symptoms may lead to working disability. Patients can be severely distressed because of functional impairment due to neuropathy.

CIPN can lead to discontinuation or dose reduction of the therapy. Concern has been raised that dose reduction and early discontinuation of the anticancer therapy might have a
negative impact on treatment response and survival (Postma et al., 2005). Patients may choose to endure the distress and limitations caused by CIPN because of fears that their cancer will progress if their chemotherapy regimen is altered or discontinued (Tofthagen et al., 2010; Bakitas, 2007).

Symptoms and signs

Depending on the substance used, a pure sensory and painful neuropathy (with cisplatin, oxaliplatin and carboplatin) or a mixed sensorimotor neuropathy with or without involvement of the autonomic nervous system (with vincristine, docetaxel and paclitaxel) can ensue (Pachman et al., 2011; Cavaletti and Marmiroli, 2010; Velasco and Bruna, 2010).

Non-painful sensory symptoms such as numbness, paresthesias and tingling are the most common initial symptoms. A few patients have neuropathic pain, even at the early course of treatment. Sensory symptoms start in feet with some chemotherapeutic agents (referring to length-dependent axonal neuropathy) whereas other agents cause simultaneous presentation of the symptoms in hands and feet (possibly referring to neuronopathy) (Bennet, 2010). Some agents (oxaliplatin, paclitaxel) cause both acute transient and chronic dose-dependent neuropathy, which presumably have different pathophysiological backgrounds. Motor neuropathy presents as distal motor weakness, and in later phase as muscle atrophy. Balance difficulties may be caused by damage of large sensory fibers (causing deteriorated proprioception) and / or distal muscular weakness. (Cavaletti and Marmiroli, 2010; Velasco and Bruna, 2010)

In sensory testing patients may have hyperesthesia (allodynia, i.e., painful response to non-painful stimuli, or hyperalgesia, i.e. increased pain sensitivity to painful stimuli) or hypoesthesia (impaired sensitivity to stimuli) or combination of them depending on the stimuli (e.g., cold allodynia combined with tactile hypoesthesia). Large sensory fiber loss results in impaired vibratory and proprioceptive sensation and decreased deep tendon reflexes. The vibratory perception threshold increases more in feet than in hands in cases of axonal damage. Small fiber neuropathy leads to abnormal findings in pinprick and thermal sensation (Swain and Arezzo, 2008; Argyriou et al., 2011).
The peripheral nervous system is targeted commonly by the toxic action of anticancer drugs and most of these act against the dorsal root ganglia (DRG) neurons or the peripheral nerve (Cavaletti et al, 2011). Little is known about the mechanisms responsible for the development of CIPN. The mechanism of neurotoxicity is not necessarily the same as of the anticancer effect, and multiple mechanisms can contribute to the neurotoxicity. Assumptions of the pathophysiological mechanisms are based mainly on animal models, and only few clinical studies have supported various hypotheses suggested by basic research.

Toxicity can affect the axons or the neuronal bodies, generally the dorsal root ganglia of the primary sensory neurons, described in cisplatin (Krarup-Hansen et al, 2007; Albers et al, 2011) and oxaliplatin (Argyriou et al, 2008b). Cisplatin is an inorganic heavy metal compound that inhibits deoxyribonucleic acid (DNA) synthesis by forming DNA adducts (McWhinney et al, 2007). The mechanism of its neurotoxicity is not known. Vinca alkaloids and taxanes are anti-microtubule agents, which bind with high affinity also to axonal microtubules.

Current view is that these drugs interfere with mitochondrial energetics, resulting in energy deficiency that leads to dysfunction of the sodium-potassium pump that maintains the normal resting potential (Bennett, 2010). As the result, the axons depolarize upnormally to the threshold necessary for spontaneous discharge. The pathophysiological mechanisms responsible for neuropathic pain are at least partly different depending on the cause of the nerve damage (Bennett, 2010).

Animal models include inflammation-based models, nerve trauma–induced models, and chemotherapy-induced models of neuropathic pain. Some scientists have recently identified abnormalities in mitochondrial structure and function in peripheral sensory fibers that are associated with neuropathic pain induced by common chemotherapeutic agents. Interestingly pain can be reversed by agents that enhance mitochondrial function. (Bennet, 2010; Zheng et al, 2011)

High doses of paclitaxel kill sensory fibers as well as motor neurons in rats, but heat hypersensitivity is very minor or absent (Bennett, 2010). Rats treated with paclitaxel, vincristine, or oxaliplatin show that both A-fibers and C-fibers have a very high incidence of abnormal spontaneous discharge (Bennett, 2010). Previous work has proposed that paclitaxel binds to microtubules making them excessively stable and inhibiting the dynamic
reorganisation of the microtubule network and cause neuronal death (Bennett, 2010). However, in the rat models, paclitaxel, vincristine, and oxaliplatin cause neither axonal nor microtubular abnormality in the saphenous nerve. All three chemotherapeutic agents cause partial degeneration of the intraepidermal sensory fibers, and the axonal mitochondria are abnormally swollen, the cristae have collapsed and the intermembrane space has expanded. Oxygen consumption in the axons of animals treated with paclitaxel is deficient, with decreased amounts of ATP produced by both respiratory complex I and complex II. (Bennett, 2010; Zheng et al, 2011)

Oxaliplatin has been shown to affect voltage-gated sodium-channel kinetics in sensory neurons, leading to sensory hyperexitability (Binder et al, 2007; Pachman et al, 2011; Park et al, 2009; Cavaletti and Marmiroli, 2010). Oxaliplatin-induced acute neuropathy is characterized by cold and mechanical hyperalgesia, leading to hypothesis that sensitization of the TRPM8 and/or TRPA1 receptors in primary afferent neurons is involved in acute oxaliplatin-induced pain (Binder et al, 2007; Stengel and Baron, 2009).

Assessment of CIPN

Clinical assessment

The mainstay of assessment of CIPN is clinical evaluation, i.e., history and clinical examination. The former includes history of symptoms (e.g., paresthesia, numbness, pain), possible predisposing factors to neuropathy (e.g., diabetes, hypothyreosis, vitamin B₁₂ deficiency and alcohol consumption) and patient’s functional capacity. The latter consists of testing of various sensory modalities (vibration, touch, joint position sense, pinprick, warm and cold), muscle strength (especially that of distal muscles, i.e., flexion and extension of wrists, walking on heel and toe), testing of deep tendon reflexes, Babinski sign, fine motoric function (e.g., buttoning) and balance (Romberg’s test, walking along line).

Grading of neurotoxicity

There is no standard universally accepted, well-validated assessment tool for CIPN. Several toxicity grading scales have been developed to score the severity of CIPN. The grading is based on symptoms and functional capacity reported by the patient and findings in physical examination. The most commonly used scale is NCI-CTC, that includes separate grading for
sensory and motor symptoms. Other grading scales used in clinical practice are the WHO (Miller et al, 1981), Eastern Cooperative Oncology Group (ECOG) (Oken et al, 1982), Ajani (Ajani et al, 1990) scales and the oxaliplatin grading scale of Levi (Levi et al, 1992; Griffith et al, 2010; Cavaletti et al, 2010). The oxaliplatin grading scale has been developed for assessing neurotoxicity caused specifically by oxaliplatin as oxaliplatin causes both acute transient and chronic neuropathy (McWhinney et al, 2009). It differs from the other scales by focusing not only on the intensity of neuropathic symptoms but also on the duration of the symptoms. It has been used, so far only for the assessment of CIPN caused by oxaliplatin. Other but above mentioned neuropathy scores are seldom used in clinical oncology practice. (Griffith et al, 2010; Cavaletti, 2009; Cavaletti et al, 2011) Patient Neurotoxicity Questionnaire (PNQ) has been developed for assess the incidence, severity of CIPN, and experiencing interference with activities of daily living (Shimozuma et al, 2009).

The Total Neuropathy Score (TNS) (Cornblath et al, 1999) is mainly used in clinical research of neurotoxicity. It is a composite measure that includes both clinical and neurophysiological components and seems to have a greater sensitivity to CIPN changes than the NCI-CTC scale (Cavaletti et al, 2010).

Assessment of neuropathic pain

The intensity of pain can be measured by VAS, numerical rating (NRS), or verbal rating (VRS) scales (Cruccu et al, 2004). VAS is one of the oldest, easiest and best validated measures to assess pain (Huskisson, 1974). Among the numerical scales the 11-point Likert scale (0 = no pain, 10 = worst possible pain) has been most widely used in recent neuropathic pain studies (Cruccu et al, 2004). Use of NRS or VAS scales is recommended both in daily practice and clinical trials (Haanpää et al, 2011). The NRS may be easier to use than the VAS for elderly people and is the most reliable to assess treatment effect in chronic pain (Dworkin et al, 2005).

The McGill Pain Questionnaire (Melzack, 1975), and the short form of it (Melzack, 1987) are the most frequently used self-rating instruments for pain measurement and also often used in treatment trials. They provide data on the various sensory and affective dimensions of pain but they are not specifically designed to assess neuropathic pain. (Cruccu et al, 2004)

Specific neuropathic assessment scales have been designed to evaluate separately the various symptoms of neuropathic pain. The Neuropathic Pain Scale (Galer and Jensen, 1997) and Neuropathic Pain Symptom Inventory (Bouhassira et al, 2004) have been validated specifically for neuropathic pain and are recommended to evaluate treatment
effects on neuropathic symptoms or their combination especially in clinical trials (Haanpää et al, 2011).

The Brief Pain Inventory is a patient-completed numeric rating scale that assesses the severity of pain (Severity scale), its impact on daily functioning (Interference scale), and other aspects of pain (location of pain, relief from medications) (Cleeland and Ryan, 1994).
Table 3. Different grading scales of CIPN.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCIC-CTC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>None</td>
<td>Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function</td>
<td>Objective sensory loss or paresthesia, interfering with function but not interfering with ADL</td>
<td>Sensory loss or paresthesia interfering with ADL</td>
<td>Permanent sensory loss that interferes with function</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>None</td>
<td>Subjective weakness but no objective findings</td>
<td>Objective mild weakness, interfering with function but not interfering with ADL</td>
<td>Moderate objective abnormality, severe functional abnormality</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Ajani</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>None</td>
<td>Paresthesia and decreased deep tendon reflexes</td>
<td>Mild objective abnormality, absence of deep tendon reflexes, mild to moderate functional</td>
<td>Severe paresthesia, moderate objective, severe functional abnormality</td>
<td>Complete sensory loss, loss of function</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>None</td>
<td>Mild transient muscle weakness</td>
<td>Persistent moderate weakness, but ambulatory</td>
<td>Unable to ambulate</td>
<td>Complete paralysis</td>
</tr>
<tr>
<td>WHO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity criteria</td>
<td>None</td>
<td>Paresthesias and/or decreased deep tendon reflexes</td>
<td>Severe paresthesias and/or mild weakness</td>
<td>Intolerable paresthesias and/or motor loss</td>
<td>Paralysis</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Decreased deep tendon reflexes, mild paresthesias, mild constipation</td>
<td>Absent deep tendon reflexes, Severe constipation, mild weakness</td>
<td>Disabling sensory loss, severe peripheral neuropathic pain, obstipation, severe weakness, bladder dysfunction</td>
<td>Respiratory dysfunction secondary to weakness, obstipation requiring surgery, paralysis confining</td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin grading scale of Levi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Paresthesia and/or dysesthesia with complete regression within one week</td>
<td>Paresthesia and/or dysesthesia with complete regression within 14 days</td>
<td>Paresthesia and/or dysesthesia with incomplete regression between courses</td>
<td>Paresthesia and/or dysesthesia with functional impairment</td>
<td></td>
</tr>
</tbody>
</table>
Laboratory tests

Electroneuromyography

In the diagnosis of polyneuropathy, electrodiagnostic studies, including nerve conducting studies and needle electromyography, are judged to be an extension of the neurological examination (England and Asbury, 2004). The combination of neuropathic symptoms, signs, and abnormal electrodiagnostic studies provides the most accurate diagnosis of distal symmetric polyneuropathy (England et al, 2005). Nerve conduction studies are essential for determining the pathophysiology of peripheral nerves. In nerve conduction studies primary demyelination is indicated by marked reduction in motor or sensory conduction velocity, conduction block or increased temporal dispersion, whereas primary axonal loss may be indicated by a decrease in amplitude of the sensory nerve action potential or the compound muscle action potential. However, electrophysiological differentiation between demyelination and axonal loss can be a challenging task as increased temporal dispersion or distal conduction block due to demyelination may result in amplitude reduction, and in axonal neuropathy loss of large fast conducting fibers may cause conduction slowing. (Tankisi et al, 2005) In practice, motor nerve conduction velocities below 40 m/s in the upper limb and 30 m/s in the lower limb generally mean demyelination. Lesser degrees of slowing of nerve conduction velocity indicate peripheral nerve damage, which could be due to axonal loss as in axonal neuropathy or neuronopathy. (Hughes, 2008)

Quantitative sensory testing

Electroneuromyography captures only large peripheral fibers. In cases of pure small fiber neuropathy electroneuromyography remains normal. In these cases quantitative sensory testing (QST) is indicated to reveal possible abnormal small fiber function.

QST analyses perception in response to external stimuli of controlled intensity. Both large (touch and vibration) and small fiber function (thermal thresholds) can be evaluated. Detection and pain thresholds are determined by applying stimuli to the skin in an ascending and descending order of magnitude. Mechanical sensitivity for tactile stimuli is measured with plastic filaments that produce graded pressures, such as the von Frey hairs, pinprick sensation with weighted needles, and vibration sensitivity with an electronic vibrometer. Thermal perception and thermal pain are measured using a thermode. (Cruccu et al, 2004) QST has been used for the early diagnosis and follow-up of small-fibre neuropathy and quantifying mechanical and thermal allostheny and hyperalgesia in painful neuropathic
syndromes. QST shows both sensory loss (i.e., hypoesthesia and hypoalgesia) and gain (i.e., hyperalgesia and allodynia) in patients with painful or painless neuropathy. QST requires standardized stimuli administration, instructions and data evaluation to achieve valid results. QST may have role in clinical trials, but is rarely used in oncological clinical practice. (Hlubocky, 2010)

Skin biopsy

Skin biopsy is being increasingly used to evaluate patients with polyneuropathy. There are different techniques for tissue processing and nerve-fibre assessment, including techniques for staining, quantification of the intraepidermal and subepidermal nerve fibers, and the use of different antibodies to distinguish nerve-fibre subtypes (Sommer and Lauria, 2007). The most common technique involves a 3 mm punch biopsy of skin from the leg. After sectioning by microtome, the tissue is stained with PGP 9.5 antibodies and examined with immunohistochemical methods. This staining allows for the identification and counting of IENF. PGP 9.5 immunohistochemistry has been validated as a reliable method for IENF density examination with good intra- and interobserver reliability in normal controls and patients with distal symmetric polyneuropathy. (England et al, 2009) The results are most commonly expressed as the number of IENF per length of section (IENF/mm). IENF density declines with age, is lower in males than in females, and is not influenced by weight or height (Gøransson et al, 2004). The sensitivity of decreased IENF density for the diagnosis of polyneuropathy is moderate to good (range 45 to 90 %). The specificity of normal IENF density for the absence of polyneuropathy is very good (range 95 to 97 %). (England et al, 2009). IENF density correlates inversely with both cold and heat detection thresholds. The European Federation of the Neurological Societies and the Peripheral Nerve Society have concluded that IENF density is a reliable and efficient technique to confirm the clinical diagnosis of small fiber neuropathy with a level A recommendation (Joint Task Force, 2010). A Finnish group has published a method of analysis of IENF (Koskinen et al, 2005).
Neurotoxic agents

The most neurotoxic chemotherapeutic agents are vinca alkaloids, cisplatin and its derivatives, and taxanes (Quasthoff and Hartung, 2002; Ocean and Vahdat, 2004). There are also other neurotoxic drugs like thalidomide and bortezomib for myeloma and ixabepilone for breast cancer (Mohty et al, 2010; Cavaletti and Marmiroli 2010). Depending on the agent, CIPN can be pure sensory and painful neuropathy (with cisplatin, carboplatin) or mixed sensorimotor neuropathy with or without involvement of the autonomic nervous system (with vincristine, taxanes, and other drugs). Both cisplatin and ifosfamide can cause acute or delayed central nervous system toxicity (Sioka and Kyritsis, 2009).

The incidence and severity of neuropathy depend on the agents, absolute dose, cumulative dose, treatment schedule, duration of infusion, and presence of concomitant medications and comorbidities (Swain and Arezzo, 2008; Carlson and Ocean, 2011).

Table 2 summarizes typical symptoms and signs of CIPN caused by different neurotoxic chemotherapeutic agents.

Table 2. Typical symptoms and signs for chronic CIPN (modified from Cavaletti et al, 2011).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Touch, thermal, pain sensation impairment</th>
<th>Vibration, position sensation impairment, ataxia</th>
<th>Neuropathic pain</th>
<th>Motor impairment</th>
<th>Autonomic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>-/+</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>-/+</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
</tr>
<tr>
<td>Vincristine</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>-/+</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

-, absent; -/+ , uncertain; +, rare; ++, common; +++ , very frequent
Microtubule targeting agents

Tubulin, a member of a small family of globular proteins, is one of the most established and clinically validated targets in oncology. Microtubules are polymeric filaments composed of α-tubulin and β-tubulin monodimers that mediate intracellular transport, signalling, and mitosis (Carlson and Ocean, 2011). They have a key role in a range of cellular functions, including cell division and growth (Swain and Arezzo, 2008). Among other things microtubules are a major component of the mitotic spindle that separates chromosomes during eukaryotic cell division. (Lee and Swain, 2006; Swain and Arezzo, 2008)

The anti-mitotic compounds are classified into two main groups: microtubule-stabilizing agents (such as the taxanes and the epothilones) and microtubule-destabilizing agents (such as the vinca alkaloids) (Swain and Arezzo, 2008). Microtubule-stabilizing agents block mitosis, and induce cell death (Lee and Swain, 2006). Whereas vinca alkaloids inhibit incorporation of tubulin into microtubules (Perez, 2009; Carlson and Ocean, 2011), the taxanes appear to inhibit microtubule disassembly by inhibiting dynamic reorganization of the microtubule network (Lee and Swain, 2006; Swain and Arezzo, 2008). Microtubule-stabilizing agents also bind with high affinity to axonal microtubules causing neurotoxicity (Swain and Arezzo, 2008; Lee and Swain, 2006). The affinity for tubulin differs among compounds and is supposed to be a reason for the distinct neurotoxic profile of these drugs. Axonal swelling in both myelinated and unmyelinated fibers leads to loss and alteration of length and arrangement of axonal microtubules (Argyriou et al., 2011; Lee and Swain, 2006; Swain and Arezzo, 2008; Carlson and Ocean, 2011).

Severe peripheral sensory neuropathy (grade 3 or 4) develops in as many as 30 % of patients treated with microtubule targeting agents (Lee and Swain, 2006). Typical clinical presentations are summarized in Table 2.

Taxanes

Taxane-based cytotoxic chemotherapies are among the most potent agents for the treatment of a variety of types of cancers including breast, lung, head and neck, gastric, prostate and ovarian cancers and are standard components of many therapeutic regimens, too (Argyriou et al., 2011; Galaal et al, 2011; Perez, 2009).
Taxanes produce frequent dose-dependent, symmetric, axonal mixed, predominantly sensory distal neuropathy. Approximately 60–90 % of the patients receiving taxanes develop mild or moderate neuropathy. Severe peripheral neuropathy (grade 3 or 4) occurs in 30 % of patients, but it is usually reversible resolving gradually after cessation of the treatment. (Lee and Swain, 2006; Argyriou et al, 2008a; Argyriou et al, 2011) Paclitaxel is more neurotoxic than docetaxel (Argyriou et al, 2011; Lee and Swain, 2006).

**Docetaxel**

Docetaxel is a semisynthetic taxoid, extracted from the European yew tree (Argyriou et al, 2008a). Common dose is 75-100 mg/m² every three weeks (q3w), 50 mg/m² biweekly and in combination treatment (carboplatin, cisplatin, cyclophosphamide, doxorubicin, capecitabine, 5-fluorouracil) usually 75mg/m². (Baker et al, 2009; Argyriou et al, 2011)

Neuropathic symptoms are usually paresthesias (skin sensation such as burning, prickling, itching or tingling), numbness, sensory loss, weakness in hands and feet. Many patients have clumsiness, loss of dexterity and unsteadiness of gait, which causes disability. (Baker et al, 2009)

In monotherapy CIPN is usually mild and predominantly sensory (Lee and Swain, 2006; Swain and Arezzo, 2008). The mean cumulative dose to onset of grade 1 or 2 neuropathy is over 371 mg/m² (Lee and Swain, 2006; Carlson and Ocean, 2011). Docetaxel at dose 100 mg/m² leads to grade 3 or 4 sensory neuropathy in 0-17 % of patients (Swain and Arezzo, 2008; Carlson and Ocean, 2011) and to motor neuropathy in 0-9 % (Lee and Swain, 2006), and at dose 75 mg/m² sensory neuropathy grade 3 or 4 occurs in 2-4 %. (Lee and Swain, 2006; Carlson and Ocean, 2011; Argyriou et al, 2008a; Argyriou et al, 2011, Vasey et al, 2004)

In adjuvant treatment with a combination of doxorubicin and docetaxel sensory neuropathy was reported in over 10 % of patients (grade 3: 0.4 %) and grade 1 motor neuropathy in less than 10 % (grade 3 to 4: 0.4 %). When using a combination of docetaxel, doxorubicin, and cyclophosphamide sensory neuropathy was reported in over 10 % (grade 3 to 4: 0 %) and motor neuropathy in less than 10 % (grade 3 to 4: 0 %). In two trials of metastatic disease treatment (docetaxel-cisplatin-5-fluorouracil) sensory neuropathy was reported in over 10 % (grade 3 to 4: 9 %) and motor neuropathy in less than 10 % (grade 3 to 4:1.3 %). When docetaxel was used in combination with prednisone sensory neuropathy was found in over 10 % (grade 3 to 4: 1 %) and motor neuropathy in less than 10 % (grade 3 to 4: 0%). It is
unproven whether corticosteroids reduce the incidence of neuropathy or not. (Baker et al; 2009).

**Paclitaxel**

Paclitaxel was originally derived from the bark of the western yew tree, Taxus brevifolia (Argyriou et al, 2008a; Ocean and Vahdat, 2004). The common dose is 175-250mg/m² (q3w) and 80-100mg/m² (weekly) (Swain and Arezzo, 2008). Infusion time can be 1, 3 or 24 hours (Lee and Swain, 2006).

Acute tingling in fingertips and toes may occur within 24 hours after paclitaxel infusion (Lee and Swain, 2006). Sensory neuropathy presents as paresthesia, numbness and burning pain appearing first in the toes and then in the fingers (Lee and Swain, 2006; Swain and Arezzo, 2008). Paresthesiae occur in distal lower extremities with a glove-and-stocking distribution and is most severe on plantar surfaces (Lee and Swain, 2006). Motor neuropathy is usually mild and presents as muscle weakness when climbing stairs. Fine motor skills may be worsened. (Argyriou et al, 2008a)

Common non-neuropathic paroxysmal pain reaction seems to involve mainly muscles (myalgia) and bones of lower extremities. It usually occurs 2 to 4 days after paclitaxel infusion and resolves typically within 5 to 6 days. Myalgia is generally mild and occurs rarely at doses below 170 mg/m². Patients receiving doses from 200 to 250 mg/m² may face myalgia more often, which tend to be mild to moderate in severity. (Carlson and Ocean 2011)

Severe neuropathy usually occurs at cumulative doses of 1,000-1,400 mg/m² (Carlson and Ocean, 2011). Neuropathy is less common with weekly regimen or lower doses per cycle (Mauri et al, 2010; Carlson and Ocean, 2011; Argyriou et al, 2011). Severe peripheral neuropathy (WHO grade 3 or 4) was reported in 7 % at dose 175 mg/m² but only in 3 % at dose 135 mg/m² (Lee and Swain, 2008). In another trial, grade 3 or 4 sensory peripheral neuropathy was observed in 33 % at dose 250 mg/m², in 19 % at 210 mg/m², and in 7 % at 175 mg/m² (Carlson and Ocean, 2011; Lee and Swain, 2008). In addition, infusion time influences neurotoxicity: severe (grade 3 or 4) neuropathy occurred in 13 % with 3 hours infusion time and in 7 % with 24 hours infusion (Argyriou et al, 2008a; Carlson and Ocean, 2011; Lee and Swain, 2008).
A randomized combination trial comparing docetaxel-carboplatin to paclitaxel-carboplatin for ovarian or peritoneal cancer showed that the former treatment was significantly less neurotoxic: grade 3 or 4 sensory neurotoxicity in 11% versus 30% and grade 3 or 4 motor neurotoxicity in 3% versus 7% (Vasey et al, 2004).

Avoiding paclitaxel cumulative doses greater than 200-250 mg/m\(^2\) and giving taxanes as a continuous infusion over 24 hours may possibly decrease the incidence of CIPN (Nahleh et al, 2010).

**Nab-Paclitaxel**

Nab-Paclitaxel is an albumin-bound 130-nm particle form of paclitaxel for breast cancer. The drug was developed to avoid the hypersensitivity reactions and peripheral neuropathy associated with the surfactant vehicles necessary in paclitaxel formulations. (Gradishar et al, 2005; Carlson and Ocean, 2011)

A randomized trial comparing nab-paclitaxel 260 mg/m\(^2\) used with every three week treatment schedule (q3w) with standard paclitaxel 175 mg/m\(^2\) showed that grade 3 sensory neuropathy was significantly more common in the nab-taxel group than in the paclitaxel group (10% vs 2%). However, it improved radiply (median 22 days). (Gradishar et al, 2005)

In a randomized study comparing nab-paclitaxel 300 mg/m\(^2\) q3w, 100 mg/m\(^2\) weekly, or 150 mg/m\(^2\) weekly or docetaxel 100 mg/m\(^2\) q3w the incidence of sensory neuropathy was more common in patients who received nab-paclitaxel q3w and 150 mg/m\(^2\) weekly regimens. The incidence of sensory neuropathy was similar in patients who received nab-paclitaxel or docetaxel, but recovery from sensory neuropathy occurred more rapidly after nab-paclitaxel compared with docetaxel. Median time to improvement in grade 3 sensory neuropathy (to grade 2 or less) was 22, 22 and 19 days for nab-paclitaxel 300 mg/m\(^2\) q3w, 100 mg/m\(^2\) weekly, and 150 mg/m\(^2\) weekly, respectively, compared with 37 days for patients who received docetaxel 100 mg/m\(^2\) q3w. (Gradishar et al, 2011)

**Cabazitaxel**

Cabazitaxel is a new semisynthetic taxane derivative. It is partially synthesized as a single diastereoisomer from 10-deacetylbaccatin III, the major natural taxoid derived from the
needles of various Taxus species. Hydroxyl groups present in docetaxel are replaced with methoxy groups in cabazitaxel. (Sartor et al, 2010; de Bono et al, 2010)

Cabazitaxel has antitumor activity in a variety of docetaxel-refractory in vitro and in vivo models. It is clinically active in women with taxane resistant metastatic breast cancer and in men with metastatic castration-resistant prostate cancer previously treated with docetaxel. The recommended cabazitaxel dose is 25 mg/m² intravenously over 1 hour on 21-day cycle in combination with oral prednisone 10mg/day. (Sartor et al, 2010)

In the randomized phase 3 TROPIC trial cabazitaxel was compared to mitoxantrone and prednisone treatment in metastatic castration-resistant prostate cancer that had progressed during docetaxel-chemotherapy. Patients with grade 2 or higher peripheral neuropathy in association with previous docetaxel treatment were excluded from the study (de Bono et al, 2010). Peripheral neuropathy (all grades) was reported during the study in 14 % patients in the cabazitaxel group and in 3 % in the mitoxantrone group. Grade 3 to 4 neuropathy was reported by 1 % in both groups. Cumulative neurotoxicity was not reported. (Sartor et al, 2010; de Bono et al, 2010; Pal et al, 2010; Oudard, 2011)

Vinca-alcaloids

Vinca alcaloids include both natural alkaloids, such as vincristine and vinblastine, and semi-synthetic compounds, such as vinorelbine and vinflunine. These are used for the treatment of acute leukemia, lymphomas, Kaposi’s sarcoma, breast, ovarian, testicular, brain and lung cancer. The affinity for tubulin differs among vinca alkaloid compounds and this biochemical property is supposed to explain the distinct neurotoxic profile of these drugs. (Argyriou et al, 2011; Cavaletti and Marmoroli, 2010)

Vincristine, a first-generation and the most toxic vinca alkaloid, is mainly used in non-Hodgkin’s and Hodgkin’s lymphoma as a part of combination chemotherapy, in treatment for leukemia, Wilm’s tumor, and sometimes as an immunosuppressant in treating thrombotic thrombocytopenic purpura or idiopathic thrombocytopenic purpura (Argyriou et al, 2011). It is supposed that vincristine causes structural changes in the microtubules by binding to tubulin and disrupting axonal transport causing primary axonal degeneration (Lee and Swain, 2006; Swain and Arezzo, 2008; Argyriou et al, 2011).

Usual vincristine dose is 1.4 mg/m² per single dose with an upper limit of 2 mg for single doses. The earliest symptoms of neuropathy develop after 5-6 mg, but considerable toxicity is commonly not seen below the cumulative dose of 15-20 mg (Argyriou et al, 2011). Mixed
sensory/motor polyneuropathy is the most common and usually dose-limiting side effect of vincristin (Sioka and Kyritsis, 2009). Nearly all patients develop some degree of neuropathy during the treatment and the neuropathy is still progressing ("coasting") in every third patients after discontinuation of the treatment (Swain and Arezzo, 2008; Carlson and Ocean, 2011). Symptoms of autonomic neuropathy include mild-to-moderate constipation; cases of paralytic ileus and megacolon have also been documented (Swain and Arezzo, 2008; Carlson and Ocean, 2011). Hepatic insufficiency is a risk factor for more severe neuropathy (Argyriou et al, 2011).

Vinorelbine is a semi-synthetic third generation vinca alkaloid inhibiting tubulin polymerisation and microtubule assembly (Aapro and Finek, 2011). It has exhibited efficacy in lung, breast, bladder, ovarian and testicular cancer (Velasco and Bruna, 2009). Common intravenous dose both in single and combination therapy is 25-30 mg/m² and administration schedule depends on the combination agent (Velasco and Bruna, 2009). Oral vinorelbine is commonly administered at the dose of 60 mg/m² once a week and at the dose of 60-80 mg/m² when used in combination on days 1 and 8 every 3 weeks (Aapro and Finek, 2011).

The vinorelbine and vinflunine-induced neuropathy is primarily sensory, usually mild to moderate in severity, cumulative, generally reversible after discontinuation and milder than the vincristine-caused neuropathy (Swain and Arezzo, 2008). The incidence of vinorelbine-induced neuropathy varies from 6 to 29 %, and grade 3 to 4 sensory neuropathy occurs in 0-6 % of patients. In the study oral vinorelbine in combination with capecitabine caused grade 3 to 4 neurotoxicity in 1 % (Swain and Arezzo, 2008; Velasco and Bruna, 2009; Carlson and Ocean, 2011; Aapro and Finek, 2011).

Vinflunine, a novel vinca alkaloid derivative for advanced breast cancer is a close analog of vinorelbine and exhibits antivascular, antiangiogenic, and antimetastatic activity (Swain and Arezzo, 2008; Argyriou et al, 2011). At common dose (320 mg/m² every 3 weeks) it seems to be even less neurotoxic than vinorelbine: in a phase II study grade 1 to 2 sensory neuropathy was reported in 13 % of the patients and no grade 3 neuropathy was seen; 3 % of the patients had grade 3 ileus (Campone et al, 2006).

Vinblastine is mostly used for Hodgkin’s disease at dose 6 mg/m² on days 1 and 8 every 28 days. Neuropathy is usually mild and occurs in 8 % (Argyriou et al, 2011).

**Epothilones**

Epothilones, a novel class of microtubule-stabilizing agents, was identified in the early 1990’ies. This class includes the natural epothilones—epothilone B (EPO906, patupilone)
and epothilone D (KOS-862) and the semisynthetic epothilone analogs ixabepilone and ZK-EPO. The epothilones are produced by the myxobacterium Sorangium cellulosum. They have potent in vitro anticancer activity, including in taxane-resistant cell lines. Their in vivo activity is, however, only moderate at most, and they have a poor metabolic stability and unfavourable pharmacokinetics. In contrast to most taxanes they have lower susceptibility to tumor resistance. Epothilones have shown prolonged remissions and improved survival in various types of refractory, treatment-resistant malignancies. (Swain and Arezzo, 2008; Argyriou et al, 2011; Carlson and Ocean, 2011)

Epothilones differ from other microtubule inhibitors in their precise binding sites and/or affinities for tubulin isoforms (Swain and Arezzo, 2008; Carlson and Ocean, 2011). Damage to the ganglion soma cells and peripheral axons through disruption of microtubules of the mitotic spindle and by interference with the axonal transport in the affected neurons may significantly contribute to the pathogenesis of epothilones-induced peripheral neuropathy. An interference with the physiological microtubule function may influence on the clinical manifestation of peripheral neuropathy, as intact microtubules are required for both anterograde and retrograde axonal transport. (Swain and Arezzo, 2008)

The primary dose-limiting toxicity of epothilones is severe diarrhea. Similar to taxanes, however, peripheral neuropathy was described as a significant nonhematological toxicity of epothilones in phase II clinical studies. Epothilones primarily produce axonal, dose-dependent, sensory distal peripheral neuropathy, which is reversible in most cases after discontinuation of the treatment. (Argyriou et al, 2011)

Epothilone-induced neuropathic symptoms and signs are commonly similar to those caused by taxanes. In studies the incidence of severe (grade 3 to 4) sensory neuropathy varies from 6 to 21 %, while neuropathy of any grade has been reported in up to 71 % of the exposed patients (Argyriou et al, 2011).

Ixabepilone

Ixabepilone was approved by the United States Food and Drug Administration (FDA) for the treatment of anthracycline- and taxane-pretreated or refractory metastatic breast cancer in 2007 (Fornier, 2007). In phase II and III trials of ixabepilone (40 mg/m² intravenously every 3 weeks) neuropathy was primarily sensory ranging from 20 % (grade 3: 1 %) in untreated early breast cancer to 67 % (grade 3: 12-20 %) in antracycline and taxane-resistant metastatic breast cancer. Neuropathy was leading to a dose reduction in 72 % of the patients (constant grade 2 or temporary grade 3 symptoms) and to permanent
discontinuation of the therapy in 21% of the patients. After a dose reduction the symptoms improved to the baseline level or to grade 1 or did not progress in 80% of the patients. The recovery took place in 6 weeks, and 70% of the patients had a total resolution within approximately 8 weeks (Fornier, 2007; Argyriou et al, 2011). A lower dose per cycle (6 mg/m²/day on days 1–5 3-weekly) might cause a lower incidence and severity of peripheral sensory neuropathy; grade 1 to 2: 52-54%, grade 3: 2% (Fornier, 2007; Argyriou et al, 2011). However, the EMA refused a marketing authorisation for ixabepilone in 2008 as the benefits of the drug in the treatment of breast cancer did not outweigh its risks. The Committee was particularly concerned over neuropathy (Argyriou et al, 2011; Fornier, 2007). It seems that second generation epothilones do not provide any improved safety in neurotoxicity compared with other microtubule-stabilizing agents (both older and newer) (Argyriou et al, 2011).

Eribulin

Eribulin mesylate is a non-taxane synthetic macrocyclic ketone analogue of halichondrin B. Although eribulin is characterized in the group of antitubulin drugs, its tubulin interactions appear to be unique: by inhibiting mitotic spindle formation, eribulin causes irreversible mitotic block, which ultimately leads to cell cycle arrest in the G2-M phase and apoptosis (Cortes, 2011). Eribulin (1.4 mg/m² intravenously q3w on day 1 and 8) is indicated in the treatment of taxane and antracycline pretreated metastatic breast cancer. In all three metastatic breast cancer phase II studies eribulin has been reported to have a low incidence of peripheral neuropathy overall, and severe peripheral neuropathy was limited to grade 3 only. (Cortes, 2011)

Platinum derivatives

Cisplatin, carboplatin, and oxaliplatin are the platinum derivatives for the treatment of colorectal, ovarian, breast, head and neck, lung, and bladder cancers, as well as lymphomas, sarcomas and germ cell tumors. Cisplatin was the first platinum derivative approved for use in anticancer therapy in 1978. Carboplatin was approved in 1989 and the third generation oxaliplatin in 2002. Cisplatin, carboplatin, and oxaliplatin differ in their solubility, chemical reactivity, oxygenated leaving groups, pharmacokinetics, and toxicity. (McWinney et al, 2009)
Platinum derivatives inhibit DNA synthesis by forming DNA adducts (McWinney et al., 2009). Primary site of neuropathy is assumed to be the involvement of large DRG cell bodies (neuronopathy) and the secondary degeneration of large, long myelinated fibers both in the limbs and in the spinal cord. Cisplatin affects axonal degeneration, but demyelination has also been reported. (Schlippe et al., 2001; Argyriou et al., 2011) Oxaliplatin affects mostly through DNA damage (Alcindor and Beauger, 2011).

The first symptoms of platinum-induced neuropathy are numbness, tingling or painful paresthesias in the hands and/or feet in a stocking-glove distribution appearing one month after initiating the treatment. In addition, patients develop subacute distal dysesthesias, areflexia, sensory ataxia and loss of proprioception and vibratory sensation. Loss of motor function has been reported in patients treated with cisplatin. DRG cell degeneration and spinal cord dorsal columns damage can cause Lhermitte’s phenomenon (an electric shock-like sensation on bending the neck) (Argyriou et al., 2011; Pasetto et al., 2006). After discontinuation of cisplatin or oxaliplatin treatment, the symptoms may still progress for up to two months (‘coasting’) (von Schlippe et al., 2001; Albers et al., 2011). Thereafter neuropathy is gradually recovering, but in case of a severe neuropathy the recovery may be incomplete (Argyriou et al., 2011; Pasetto et al., 2006).

Symptoms and signs are symmetric and generally more severe distally. In neurological examination reduced vibration and joint position sensations (evidence of large fibre sensory loss) and diminished or absent muscle stretch reflexes can be found. Decreased pinprick sensation is a consequence of diminished small fibre sensation. Severe proprioceptive loss may present as sensory ataxia leading to functional disability. (von Schlippe et al., 2001; Albers et al., 2011; Swain and Arezzo, 2008)

In nerve conduction studies done in patients receiving oxaliplatin, neurophysiological features of neuropathy became evident despite the lessening of symptoms. Because of this it is suggested that a reduction in ‘positive’ symptoms (such as pain and paraesthesiae) might be related to large fibre loss, which may occur concurrent with the development of ‘negative’ features such as numbness (Kiernan, 2007). Abnormalities in sodium channels, mitochondrial dysfunction and DRG cell atrophy due to accumulation of platinum compounds are suggested to explain axonal degeneration (Cavaletti and Marmiroli, 2010, Argyriou et al., 2011). The typical clinical features of platinum derivatives are summarized in Table 2.
**Cisplatin**

Cisplatin is the first heavy metal used as an antineoplastic agent since the early 1970’sies to treat lung, ovarian, testicular, bladder, head and neck, endometrial and breast cancer. Dosage used in clinical practice varies between 50 to 100 mg/m² given intravenously every three to four weeks and 20 mg/m² daily for 5 days or weekly. (Albers et al, 2011)

The incidence and severity of neurotoxicity are mainly determined by the cumulative cisplatin dose. The incidence of neuropathy varies between 30 % and 100 % (median 57 %). With cumulative dose 300–400 mg/m² up to 64 % of the patients have grade 3 to 4 peripheral neuropathy (Velasco and Bruna; 2009, Argyriou et al, 2011; Albers et al, 2011). Generally the symptoms appear in 85 % of the patients at cumulative doses 300-600 mg/m². (von Schlippe et al, 2001; Albers et al, 2011; Argyriou et al, 2011)

The symptoms of cisplatin-induced neuropathy appear as numbness, tingling or painful paresthesias in one month, progressing during and even after the treatment (‘coasting’) to areflexia and sensory ataxia. Lhermitte’s symptom and/or muscle cramps have been described. Motor symptoms may occur with high doses. Recovery is slow, and cisplatin-induced neuropathy is irreversible in approximately 30–50 % of patients. (Albers et al, 2011; Argyriou et al, 2011)

**Oxaliplatin**

Oxaliplatin is widely used in treatment of colorectal cancer. It has also been studied in other gastrointestinal malignancies like gastroesophageal and pancreatic cancers. Currently recommended doses for oxaliplatin are 85 mg/m² daily every 2 weeks, 130 mg/m² daily as a 2–6 hour infusion every 3 weeks or 175 mg/m² daily as a chronomodulated infusion every 3 weeks. (Pasetto et al, 2006)

Oxaliplatin produces both a reversible acute and partly irreversible cumulative neuropathy, which are two distinct clinical syndromes. The acute neuropathy is characterized by cold-related and transient sensory paresthesia and dysesthesia in mouth, throat, perioral region, and upper limbs, and by motor cramps and/or muscle spasms in throat muscles. The dose-limiting cumulative peripheral sensory neuropathy has the typical features of platinum drug-induced peripheral neuropathy. (Velasco and Bruna, 2010; Pasetto et al, 2006)
Acute symptoms are very common, experienced by 60-90 % of the patients. The acute neuropathy occurs during or after the infusion within the next few days. The muscular symptoms are triggered or enhanced by exposure to cold. A smaller number of patients experience slurred speech, jaw pain during chewing, paresthesias in the limbs or calf cramps when walking. These symptoms can last for days to weeks. One of the most fearful symptoms is pharyngo-laryngo-dysesthesia accompanied by a sensation of shortness of breath without any objective evidence of respiratory distress. Usually it is transient lasting from a few seconds to a few hours. It may be cold-triggered and may increase in both duration and severity with repeated administration. Acute neuropathy is always reversible (Velasco and Bruna, 2010; Pasetto et al, 2006). The acute neurotoxicity is explained as a functional chanellopathy of axonal sodium channels (Park et al, 2009).

Oxaliplatin induces also cumulative distal neurotoxicity, which can be irreversible. The dose-limiting, cumulative sensory neurotoxicity is seen in 10–15 % of patients after cumulative doses of 780–850 mg/m^2 (de Gramont et al, 2000), however, 74 % of patients recovered from grade 3 neurotoxicity. The median recovery time is 13 weeks, but symptoms can persist even for 2 years or more in up to 10 % of the patients. The risk of permanent neuropathy is significantly increasing at cumulative dose over 1,000 mg/m^2. Cumulative neurotoxicity causes dose reductions or discontinuation of the therapy relatively often (in 20 % of the patients after 6 cycles, in 38 % after 9 and in 63 % after 12 cycles). (Kiernan, 2007; Mitchell et al, 2006; Velasco and Bruna, 2010; Pasetto et al, 2006)

The treatment schedule has also influence on the risk for peripheral neuropathy. Based on indirect comparisons, oxaliplatin with weekly bolus of 5-fluorouracil and leucovorin (FLOX) seemed to cause less grade 3 neuropathy (8 %) than with continuous 5-fluorouracil and leucovorin (FOLFOX) (12 %), but there is no direct comparison study. A randomized trial of FOLFOX 4 versus scheduled intermittent oxaliplatin (OPTIMOX 1) was associated with a slight reduction in grade 3 neuropathy (18 % versus 13 %). The combination of oxaliplatin (130 mg/m^2) either with capecitabine (XELOX) or with infusional 5-fluorouracil regimen (FOLFOX4) caused equally neuropathy (grade 3 or 4 neurotoxicity 17 %). (Pasetto et al, 2006; Alcindor and Beauger, 2011)

**Carboplatin**

Carboplatin is used as a treatment for ovarian and lung cancer. It is typically used in combination with another chemotherapeutic agents like taxanes, vinorelbine, etoposide or gemcitabine. As compared to other platinum derivatives, neurotoxicity is less frequent (4 to 6
and relatively mild. The risk of neurotoxicity is more dependent on the partnering agent. Risk of carboplatin-induced peripheral neurotoxicity increased in patients older than 65 years and in patients previously treated with cisplatin. (McWhinney et al, 2009)

**Bortezomib, thalidomide and lenalidomide**

Bortezomib, thalidomide and lenalidomide are used in treatment of multiple myeloma. Bortezomib is a proteasome inhibitor, whereas thalidomide and lenalidomide suppress the synthesis of tumor necrosis factor alfa (TNF-α) (Mohty et al, 2010).

**Bortezomib**

Bortezomib is the first proteasome inhibitor to be investigated in humans. Bortezomib-induced peripheral neuropathy appears to be a proteasome-inhibitor class effect. At the molecular level, mitochondrial and endoplasmic reticulum damage seems to play a key role in bortezomib-induced peripheral neuropathy, since bortezomib is able to activate the mitochondrial-based apoptotic pathway (Mohty et al, 2010; Pei et al, 2004). Some autoimmune or inflammatory factors can be triggers for the apoptotic process. (Richardson et al, 2006; Mohty et al, 2010)

Bortezomib-induced neuropathy is length-dependent, sensory, axonal polyneuropathy and affects especially small fibers. The symptoms are pain, paresthesia, burning sensation, dysesthesia, numbness and sensory loss, affecting feet more than hands in a stocking-and-glove distribution. Changes in proprioception can also occur. Motor impairment is rare (less than 10 %). Orthostatic hypotension has been reported in 10 % of the patients (grade 3: 4 %). (Mohty et al, 2010)

Bortezomib-induced neuropathy typically occurs within the first treatment cycles and does not increase significantly thereafter. Overall incidence of peripheral neuropathy is up to 40 % (30 % grade 1 to 2: 30 %, grade 3 to 4: less than 10 %). However, some patients develop severe symptoms immediately after starting bortezomib. The symptoms do not disappear between the treatment cycles. (Richardson et al, 2006; Mohty et al, 2010)

The neurotoxicity depends on the route of administration (neurotoxicity in 38 % of the patients with subcutaneous vs. 53 % with intravenous administration) (Moureau et al, 2011), treatment schedule (intervals between the cycles, low-dose weekly vs. three-weekly schedule), dose per cycle (1 mg/m² vs 1.3 mg/m²) and total dose (Mohty et al, 2010;
Richardson et al, 2006). The concomitant use of other agents, in particular the addition of thalidomide, seems surprisingly not to affect the risk of bortezomib-induced peripheral neuropathy. It is possible that thalidomide has a protective effect with respect to bortezomib through its anti-inflammatory action that inhibits TNF-α. Bortezomib-induced peripheral neuropathy seems to recover after discontinuation or reduction of doses within some months (Mohty et al, 2010).

**Thalidomide**

In the late 1950’ies thalidomide was used as a sedative–hypnotic agent, but because of its teratogenic effects it was withdrawn in 1961. Later, the therapeutic use of talidomide has been reintroduced in the treatment of many dermatologic, gastrointestinal, rheumatologic, and oncologic conditions. (Plasmati et al, 2007) Common single dose is 200 mg a day (Ghosh and Ghosh, 2010).

The mechanisms of thalidomide-induced peripheral neuropathy are not clear. Thalidomide causes reduction in nerve blood supply due to the anti-angiogeneic properties. Variations in genes involved in drug’s neurotoxicity are likely to have an impact on whether an individual patient will develop this adverse effect (Cavaletti and Marmiroli, 2010; Mohty et al, 2010).

Thalidomide causes mostly mixed sensory-motor axonal neuropathy. It affects mainly small sensory fibers, but also in some extent large fibers. Motor impairment is rare but possible in the most severe cases. The clinical manifestations include bilateral and symmetrical sensory disorders, rarely motor disorders or dysautonomia. Symptoms are distal paresthesia and hyperesthesia that initially affect the toes, sometimes the fingers, and that may extend proximally. Trembling is common but usually doesn’t affect daily activities. Later vibratory sensitivity and proprioception may be affected, leading to progressive ataxia, difficulty in walking and trembling when posture is maintained (Cavaletti and Marmiroli, 2010; Mohty et al, 2010).

The overall incidence of thalidomide-induced peripheral neuropathy ranges from 25 to 83 %, of which two thirds is grade 1 to 2 and one third grade 3 to 4. Approximately 15 % of the patients interrupt thalidomide treatment due to neuropathy (Mohty et al, 2010). In a meta-analysis of 42 phase II trials of single thalidomide in 1674 relapsed or refractory multiple myeloma patients, the incidence of grade 3 to 4 peripheral neuropathy was 6 % (Mohty et al, 2010). The neurological complications usually occur after prolonged exposure: 70 % of the
patients treated for 12 months or more will develop peripheral neuropathy, which often limits the dose and the duration of treatment (Cavaletti and Marmiroli, 2010). To minimize the risk of irreversible neuropathy, thalidomide administration must be reduced or discontinued before the sensory neuropathy becomes painful, complicated by motor deficiency or interferes with daily activities (Sioka and Kyritsis, 2009; Mohty et al, 2010).

**Lenalidomide**

Lenalidomide is an analogue of thalidomide with a better inhibition of TNF-α and milder neurotoxicity (Behin et al, 2008; Mohty et al, 2010). Neurotoxicity of oral lenalidomide depends on a treatment schedule, 30 mg once a day being more toxic (23 %) than 15 mg twice daily (10 %). Only 3 % of patients developed grade 3 neuropathy. Pre-existing thalidomide treatment seemed not to increase the risk of neurotoxicity. (Behin et al, 2008)

**Prevention of CIPN**

Prevention of CIPN by a concomitant agent would be a worthy option to enable effective cancer treatment with neurotoxic chemotherapeutic agents. The ideal preventive treatment is effective (i.e., it should prevent or slow the progression of CIPN), well tolerated, and not compromising antitumor effect of the cancer treatment (Gamelin et al, 2004; Hochster et al, 2007). In spite of promising animal studies, no effective preventive agent with strong evidence of its efficacy is available for clinical use.

**Amifostine**

Amifostine is an organic thiophosphate that acts as a scavenger of oxygen free radicals and shows selective protection for normal tissues against toxicities induced by radiation, alkylating agents and platinum compounds (Ocean and Vahdat, 2004; Kaley and Deangelis, 2009; Albers et al, 2011). Four randomized controlled studies (541 total participants) have been performed in prevention of neurotoxicity: cisplatin for advanced head and neck (Planting et al, 1999), paclitaxel and carboplatin for non-small cell lung cancer (Kanat et al, 2003), paclitaxel and carboplatin for ovarian cancer (Lorusso et al, 2003) and cisplatin and cyclophosphamide for advanced ovarian cancer (Kemp et al, 1996). One of these trials reported benefit of amifostine in neuroprotection (Planting et al, 1999). In all studies patients
randomized to the amifostine groups received intravenous amifostine immediately before chemotherapy at doses of 740 mg/m² or 910 mg/m², and chemotherapy was given either weekly or every three weeks up to six cycles (Kaley and Deangelis, 2009; Albers et al., 2011). There was no equal or standardized neurological examination scale among these studies; different clinical scales based on descriptions of conventional neurological symptoms or signs (Planting et al., 1999; Kanat et al., 2003; Lorusso et al., 2003), activities of daily living (Kanat et al., 2003) or NCIC-CTC (Kemp et al., 1996) were used. None of these four trials clearly masked the participant or the observer (Albers et al., 2011). According to the results published so far the clinical benefit of amifostine is still unclear in spite of some positive effects (Hensley et al., 2009; Albers et al., 2011). Because several of amifostine studies used a combination of carboplatin and paclitaxel, the American Society of Clinical Oncology panel extended recommendation against using amifostine for prevention of platinum-associated neurotoxicity or ototoxicity or prevention of neuropathy caused by paclitaxel or cisplatin (Hensley et al., 2009).

Acetyl-L-carnitine

Acetyl-L-carnitine has an essential role in intermediary metabolism including neuroprotective and neurotrophic actions, antioxidant activity, positive actions on mitochondrial metabolism, and stabilization of intracellular membranes (de Grandis, 2007). Acetyl-L-carnitine improves non-oncological neuropathies (Bianchi et al., 2005). All patients except one reported symptomatic relief in a pilot study with oral acetyl-L-carnitine (1 g twice a day) for 8 weeks in 25 patients with severe neuropathy (grade 3 or persisting grade 2) during paclitaxel or cisplatin therapy. The sensory neuropathy grade improved in 60 %, and motor neuropathy in 79 %. (Bianchi et al., 2005) No significant difference was found in overall peripheral neuropathy incidence between treatment groups in the randomized placebo-controlled REASON study in prevention of sagopilone-induced neuropathy with acetyl-L-carnitine (1 g twice a day) in 150 ovarian and prostata cancer patients. However, the incidence of high-grade neuropathy in the ovarian cancer patients was significantly lower in the acetyl-L-carnitine group than in the placebo group (grade 2 35 % vs. 19 %, grade 3 20 % vs. 38 %) in subanalyses (Lhomme et al., 2011). Further data is needed to validate these results.
**Vitamin E**

Alpha-tocopherol is the most common lipid-soluble, chain-breaking antioxidant in the body and it protects the integrity of membranes by inhibiting lipid peroxidation. A primary mechanism of chemotherapy-induced toxicity is the formation of reactive oxygen species or free radicals. Antioxidants may protect against neurotoxicity by bonding to free radicals and preventing oxidative damage. Although the mechanism of vitamin E-mediated neuroprotection is not entirely known, there are some similarities between clinical and neuropathological aspects in peripheral neuropathy induced by cisplatin and vitamin E deficiency (Sioka and Kyritsis, 2009; Kaley and Deangelis, 2009; Kottscahde et al, 2011). In addition, during cisplatin therapy serum levels of vitamin E have been decreased. (Sioka and Kyritsis, 2009; Albers et al, 2011; Wolf et al, 2008)

In a randomized pilot study of 47 patients alpha-tocopherol 300 mg/day before and during cisplatin treatment and afterwards for 3 months, a significantly decreased incidence of peripheral neuropathy was seen (31 % vs. 86 %) (Pace et al, 2003). These results were later repeated in a randomized double-blind study of 108 cisplatin-treated patients. In that study alpha-tocopherol was given 400mg/day. The incidence of neurotoxicity was significantly lower in the vitamin-E group than in the placebo group (6 % vs. 42 %), and the severity of neurotoxicity (measured with TNS) was significantly lower in the vitamin E group than those receiving placebo (mean TNS 1.4 vs 4.1). (Pace et al, 2010)

In another phase III randomized double-blind placebo controlled trial of 207 patients vitamin E 400 mg twice daily did not make any difference in the incidence of grade 2 sensory neuropathy (Kottschade et al, 2010). Thus, the results are still inconclusive and there is concern that supplemental antioxidant might interfere with the oxidative breakdown of cellular DNA and cell membranes necessary for cytotoxic agents to work. (Wolf et al, 2008)

**Carbamazepine and oxcarbazepine**

Altered sodium channel inactivation kinetics has been shown in rat sensory nerves in the development of acute neuropathy during oxaliplatin administration. Carbamazepine, a sodium channel blocker, could therefore be an antagonist drug. Carbamazepine should, however, be given before the first dose of oxaliplatin because channel inactivation kinetics cannot be reversed by washout of oxaliplatin. (von Delius et al, 2007)
A pilot study of 40 patients showed that oxaliplatin-induced sensory neuropathy may be prevented by carbamazepine; carbamazepine pretreated patients reached significantly higher cumulative oxaliplatin doses (Lerch et al, 2002). However, in a randomized controlled study of 36 patients carbamazepine 200 mg did not prevent neurotoxicity; no significant differences in grade 3 and 4 neurotoxicity were found. (von Delius et al, 2007)

Oxcarbazepine blocks sodium currents, but it also modulates different types of calcium channels avoiding metabolites causing adverse effects. In a randomized, open-label, controlled trial of 32 patients with colon cancer treated with FOLFOX-4 the incidence of neuropathy was lower in patients receiving oxcarbazepine 600mg twice daily (31 % vs. 75 %) (Argyriou et al, 2006). The trial was rather small and open, which reduces its value (Wolf et al, 2008)

Thus the evidence of carbamazebine and oxcarbazine in prevention of CIPN is still lacking.

**Xaliproden**

Xaliproden is an orally active, non-peptide neurotrophic and neuroprotective 5-HT (1A) receptor agonist. It increases the expression of neurotrophins such as nerve growth factor, brain derived neurotrophic factor, and neurotrophin 3, and acts on the development and repair of neurons. In a prospective, randomized, double-blind placebo controlled phase III study of 649 patients with metastatic colorectal cancer who were treated with oxaliplatin and xaliproden (1 mg/day) no overall reduction of neurotoxicity was seen, but 5 % of patients were shifted from grade 3 to grade 2 neurotoxicity. The use of xaliproden was neither associated with a higher cumulative oxaliplatin-dose nor a longer time on therapy. (Wolff et al, 2008)
Glutamine

Glutamine is a nonessential amino acid. Glial cells release glutamine, which is then taken up into presynaptic terminals and metabolized into glutamate by glutaminase (a mitochondrial enzyme). Glutamate is an important neurotransmitter that plays a key role in long-term potentiation and is important for learning and memory. (Vahdat et al, 2001; Amara, 2008; Ocean and Vahdat, 2004; Kaley and Deangelis, 2009)

As a neuroprotective agent glutamine was studied in two pilot trials. One trial estimated the impact of oral glutamine on high-dose paclitaxel-induced peripheral neuropathy (paclitaxel 825 mg/m² over 24 hours) (Vahdat et al, 2001). Twelve patients were given oral glutamine 10 g 3 times a day for 4 days, beginning 24 hours after the completion of paclitaxel and 33 did not receive glutamine. In the glutamine group there were significantly fewer moderate-to-severe dysesthesias, numbness and fewer abnormal gait, reduction of vibration sense in the toes, motor weakness and less interference with ADL compared with non-glutamine patients. However, all these toxicities were reversible over time. The result of another small study of 46 patients was in line with the previous one (Stubblefield et al, 2005). In the third randomised, open label trial of 86 oxaliplatin treated patients with metastatic colorectal cancer oral glutamine was given as 15 g twice daily for seven consecutive days every 2 weeks following oxaliplatin infusion. Patients with glutamine had significantly fewer symptoms and interference with ADL: grade 3 to 4 neuropathy after four cycles (5 % vs. 18 %) and six cycles (12 % vs. 32 %), and the glutamine group needed fewer oxaliplatin dose reductions. There were no significant differences in response rate to oxaliplatin or median survival time. (Wang et al, 2007)

All three clinical trials specified that oral glutamine prevents various common signs and symptoms of CIPN. However, the studies were small and none of them were placebo-controlled. Glutamine was well tolerated. However, glutamine may increase the risk of seizures and reduce the efficacy of antiepileptic medications. Further placebo-controlled trials are necessary. (Amara, 2008; Wolf et al, 2008)
**Glutathione**

A naturally occurring tripeptide glutathione has a high affinity for heavy metals and in animal models it has been shown to decrease accumulation of platinum in the DRG (Pachman *et al.*, 2011).

There are altogether six prospective, randomised placebo controlled studies of a total of 354 participants. Three of them used cisplatin for ovarian cancer, one cisplatin for non-small cell lung cancer and head and neck cancer and two trials oxaliplatin for colorectal cancer. The glutathione dose varied from 1.5 g/m² to 5 g before chemotherapy. (Pachman *et al.*, 2011; Albers *et al.*, 2011) Five studies reported a significant protective effect of glutathione. However, the data is insufficient to make any conclusions given the variable dosages used with different malignancies, different combinations of chemotherapies, limited statistics, and lack of long-term follow-up. (Albers *et al.*, 2011)

**Org 2766**

The peptide Org 2766 is a synthetic ACTH (4–9) analogue devoid of the adrenocorticotropic and melanotropic effects. In preclinical tissue culture studies Org 2766 has delayed or even prevented cisplatin induced neuropathy without causing side effects or interfering with oncological activity. It promoted neurite outgrowth in the absence of nerve growth factor. (Albers *et al.*, 2011)

There are three studies (188 Org 2766 treated participants and 123 controls) of Org 2766 in prevention of neurotoxicity. Org 2766 was given subcutaneously from 0.25 to 4.0 mg/kg. The combined data of three trials using the same measure found no significant group difference in QST examination. The overall results are to be considered as negative, because the first study suggesting a protective effect of Org 2766 was based on an inadequate statistical analysis. (Albers *et al.*, 2011; Pachman *et al.*, 2011)
Calcium and magnesium infusions

The strongest data in prevention of CIPN is from intravenous calcium and magnesium infusions in oxaliplatin treated patients. Oxaliplatin acute toxicity has been hypothesized to be related to the interference of oxalate, a metabolite of oxaliplatin and a calcium chelator, with voltage-gated sodium channels (Pachman et al, 2011). Increasing concentration of extracellular calcium facilitates sodium channel closing, and this decreases the oxaliplatin-induced hyperexcitability of peripheral neurons. (Grothey et al, 2011)

In the first retrospective, non-randomised report of 96 patients with advanced colorectal cancer who had received intravenous calcium gluconate 1 g and magnesium sulphate 1 g before and after oxaliplatin and 65 control patients the median cumulative administered oxaliplatin dose was 910 mg/m² in the Ca/Mg group compared with 650 mg/m² in the control group. In the Ca/Mg group 4 % of patients discontinued chemotherapy due to neurotoxicity compared to 31 % of the control group. Patients receiving Ca/Mg did not suffer laryngopharyngeal dysaesthesia whereas 9 % of the control patients did. At the end of the study 27 % of the Ca/Mg group vs 75 % of the control group had signs of neurotoxicity of any grade. Grade 3 neurotoxicity was less frequent in the Ca/Mg (8 % vs. 20 %) than in the control group. (Gamelin et al, 2004)

Thereafter, three randomized placebo controlled trials have repeated these results (Grothey et al, 2011). In the first study (N04C7) significantly less grade 2 or greater neurotoxicity was found in Ca/Mg group than in the placebo group (22 % vs. 41% by the NCI-CTC, and 28 % vs. 51 % by the oxaliplatin neuropathy scale), but no effect on acute cold-induced sensory neuropathy was seen (Grothey et al, 2011). In the second study (CONcePT) final results are not yet available. Finally, in a preliminary report of the third study (French Neuroxa ) a significantly lower frequency and grade of oxaliplatin neurotoxicity was found in Ca/Mg group (5 % vs. 24 % grade 3 NCI-CTC). (Gamelin et al, 2008; Grothey et al, 2011)

There have been some concerns of the safety of Ca/Mg infusions. In the interim analyses of the CONcePT trial (N=174) oxaliplatin response rate was impaired in Ca/Mg group. Thus the CONcePT trial and also N04C7 (N= 104 of 300 planned) and phase II Asian trials were prematurely interrupted. Afterwards the response rate by an independent blinded radiologic review of radiologic scans was actually higher in the Ca/Mg group than in the placebo group (Grothey et al, 2011). In French Neuroxa study there was no affect on the oxaliplatin response rate (Gamelin et al, 2008).
So far, there is still lack of consensus whether Ca/Mg infusions are truly effective as neuroprotective agent against oxaliplatin-induced sensory neurotoxicities. (Grothey et al, 2011)

**Melatonin**

Melatonin, a pineal hormone, has been examined as a neuroprotective drug in preclinical and clinical studies. It is suggested that melatonin inhibits the production of free radicals, which play a role in mediating the toxicity of chemotherapy. There are only few preliminary reports available of melatonin in prevention of CIPN with some positive results. (Lissoni et al, 1997a; Lissoni et al, 1997b)

In an open label, phase II pilot study of 22 breast cancer patients initiating taxane chemotherapy with melatonin (21 mg/day) neuropathy was seen in 46 % (10 patients). Twentythree % (5 patients) had grade 1 and 23 % (5 patients) had grade 2 neuropathies (Nahleh et al, 2010). No grade 3 or 4 neuropathy was reported. In another pilot study of 80 patients neuropathy was less frequent in patients treated with melatonin. The effectiveness of chemotherapy was not altered by the addition of melatonin. (Lissoni et al, 1997b; Nahleh et al, 2010)

In line with previous two pilot studies, a randomized study of 70 patients with non-small cell lung cancer patient receiving cisplatin and etoposide, melatonin 20 mg daily showed significant reduction in the frequency of neuropathy (0/34 vs. 5/34 patients). There was no impact on the effectiveness of the chemotherapy regimen, on the contrary, the one year survival for patients receiving melatonin was better. (Lissoni et al, 1997b; Nahleh et al, 2010)

**Other agents**

In animal studies erythropoietin has showed neuroprotective and neurotropic effects and efficacy in the prevention and treatment of CIPN, mostly in cisplatin-induced neuropathy. However, the concern of the safety of erythropoietin in cancer treatment should be taken seriously. (Pachman et al, 2011)

Neurosteroid allopregnanolone, also known as 3α,5α-tetrahydropregosterone, is a metabolite of progesterone and it interacts with various receptors and channels, including GABA-A receptors and calcium channels. Allopregnanolone has neuroprotective, neurogenic, and analgesic effects. In two animal studies the animals treated with neurosteroids had lesser alterations in peripheral nerves, such as nerve conduction velocity
and pain-transmission abnormalities. The safety of using neurosteroids in patients with hormone-dependent cancers is unknown. (Pachman et al, 2011)

A calcium channel antagonist nimodipine has been reported to have neuroprotective activity in animal studies. However, in a pilot study of 50 patients treated with cisplatin no neuroprotective effect was seen. (Pachman et al, 2011)

In a phase II randomized controlled prevention study the recombinant human leukemia inhibitory factor did not succeed to show any benefit in patients treated with carboplatin/paclitaxel (Pachman et al, 2011).

Diethyldithiocarbamate has been reported to block cisplatin-induced toxicity in animal studies. However, in a clinical study of 221 cancer patients there was no significant neuroprotective effect of diethyldithiocarbamate (Gandara et al, 1995). The data suffers from having no measures of neurotoxicity other than subjective reporting (Albers et al, 2011).

The anticonvulsant valproate showed efficacy in cisplatin-treated rats and was associated with improved sensory-nerve conduction velocity and DRG neuronal survival (Pachman et al, 2011). No clinical trials are available.

Interleukin-6 is a cytokine that has been investigated in animal models for prevention and treatment of diabetic neuropathy and CIPN in animal models (Pachman et al, 2011).

Several studies of the efficacy of antioxidants or their combinations have been done, but no effect has been proven so far. (Albers et al, 2011; Kaley and Deangelis, 2009; Velasco and Bruna, 2010; Botez and Hermann, 2010; Pachman et al, 2011)

Treatment of CIPN

There is no standard treatment of CIPN, unless it involves pain. So far, there are no treatments that have been shown to be efficacious in randomized controlled trials. On the basis of pathophysiological mechanisms, potential therapeutic targets for treatment of CIPN would be sodium channels, calcium channels, TRPV1, gamma amino butyric acid receptors, serotonin and norepinephrine receptors, N-methyl-D-aspartate receptors, and α-receptors. (Pachman et al, 2011)
Acetyl-L-carnitine

According to animal studies acetyl-L-carnitine could be effective in prevention and/or treatment of paclitaxel-induced peripheral neuropathy. In a pilot trial of 25 patients with grade 3 neuropathy from paclitaxel or cisplatin, acetyl-L-carnitine showed some positive effect, but further studies are needed. (Bianchi et al, 2005; Ocean and Vahdat, 2004; Kaley and Deangelis, 2009; Cavaletti, 2009; Pachman et al, 2011; Albers et al, 2011)

Alpha-lipoic acid

Alpha-lipoic acid is an antioxidant produced naturally by the body. It is included in some foods and in nutritional supplements. In vitro studies have shown alpha-lipoic acid protecting sensory neurons through its anti-oxidant and mitochondrial regulatory functions (Melli et al, 2008). Four-year treatment with alpha-lipoic acid in mild-to-moderate diabetes-induced neuropathy reportedly leads to a clinically meaningful improvement and prevention of progression of neuropathic impairments while being well tolerated (Ziegler et al, 2011). There is a phase II trial ongoing in breast cancer patients treated with paclitaxel. (Melli et al, 2008; Pasetto et al, 2006)

Anticonvulsants: gabapentin, pregabalin and lamotrigine

Anticonvulsants are commonly used in painful diabetic neuropathy, nerve injury pain, PHN, trigeminal neuralgia, phantom limb pain. Gabapentin provides significant pain relief approximately for a third of the patients with painful neuropathy. The most common side-effects are dizziness, somnolence, peripheral oedema, and gait disturbance. (Moore et al, 2011)

The most commonly used anticonvulsants are gabapentinoids, gabapentin and pregabalin. Gabapentinoids bind on α2-δ subunit of presynaptic, voltage-gated calcium channels reducing calcium influx and neurotransmitter release from damaged hyperexcited neurons. (Moore et al, 2011)
In a double-blind placebo-controlled trial of 115 patients with CIPN gabapentin (target dose 900 mg three times a day) for 6 weeks did not significantly improve the pain relief or the ECOG toxicity rating for sensory neuropathy (Rao et al, 2007).

In animal studies intraperitoneally given pregabalin has caused a significant reduction of the vincristine induced allodynia (Nozaki-Taguchi et al, 2001). In a small study of 23 gastrointestinal cancer patients with grade 2 and 3 oxaliplatin-induced sensory neuropathy pregabalin (target dose of 150 mg three times a day) reduced the neuropathy to grade 1-2 in 48 % of the patients (Saif et al, 2010). The target dose provided the best benefit, but there was some efficacy at lower doses also (Pachmann et al, 2011).

Lamotrigine failed to demonstrate any significant impact on neuropathic pain in a study of 125 patients with oxaliplatin induced neuropathic pain. (Rao et al, 2007; Wiffen et al, 2011)

**Antidepressants: tricyclic agents, duloxetine and venlafaxine**

In the treatment of neuropathies, especially in diabetic neuropathy and PHN, tricyclic antidepressants are the most effective and widely used antidepressants (number needed to treat 3,60, 95 % CI 3 to 4.5) (Saarto and Wiffen, 2010). Amitriptyline has been shown to be superior to placebo in treatment of diabetic neuropathy (Max, 1987), postherpetic neuralgia (Graff-Radford et al, 2000), and postoperative neuropathic pain in breast cancer patients (Kalso et al, 1996). There are also some new data on venlafaxine and duloxetine in the treatment of neuropathic pain (Saarto and Wiffen, 2010, Durand et al, 2011; Bril et al, 2011).

Duloxetine hydrochloride is a balanced SNRI used in the treatment of major depression. Its efficacy is established by three large-scale trials in diabetic painful polyneuropathy (Attal et al 2010). Duloxetine is approved by the FDA for the management of diabetic peripheral neuropathy and fibromyalgia, as well as for depression and anxiety. (Yang et al, 2011) In a single-arm open-labeled pilot study of 39 patients with stage III or IV colorectal cancer and chronic oxaliplatin-induced neuropathy duloxetine (30 - 60 mg/day) improved VAS score in 19 patients (63 %), among them, nine (47 %) patients showed a simultaneous improvement in NCI-CTC neurotoxicity grade (Yang et al, 2011). However, nine patients (28 %) discontinued duloxetine because of adverse events, including dizziness/giddiness/nausea, somnolence, restlessness or insomnia and urinary hesitancy. There is an ongoing phase III double blind trial of oral duloxetine for treatment of pain associated with CIPN (http://clinicaltrials.gov). Of note, duloxetine is a potent cytochrome P450 2D6 inhibitor, and hence it might interfere with other drugs metabolized via same pathway (e.g., tamoxifen).
Duloxetine has been reported to lower the plasma concentration of endoxifen, the active form of tamoxifen (Yang et al., 2011; Pachman et al., 2011).

Venlafaxine is a SNRI antidepressant with reported efficacy for painful neuropathies of various ethiologies (Pachman et al., 2011). In treatment of various neuropathies venlafaxine has been shown to have pain-relieving effects only at high doses (150–225 mg/day), when noradrenergic effect is more predominant and accompanied with more side effects, too (Pachman et al., 2011).

In a randomized, double-blind, placebo-controlled phase III trial (EFFOX) of 48 cancer patients with oxaliplatin-induced acute neurotoxicity venlafaxine 50 mg or placebo was given orally one hour prior to oxaliplatin infusion and extended-release venlafaxine 37.5 mg or placebo twice a day from day 2 to day 11. In the venlafaxine group there was significantly less acute neurosensory pain than in the placebo group (35 % vs. 77 %). Full relief of pain (measured by NRS) was reported in 31 % of the patients in venlafaxine arm vs. 53 % in the placebo arm. The most common side effects of venlafaxine are somnolence, nausea, asthenia, and at higher doses hypertension may occur. (Durand et al., 2011)
AIMS OF THE PRESENT STUDY

In patients treated with neurotoxic chemotherapy, the present study aimed to investigate:

1. The prevalence and discomfort of neurotoxicity in relation to other adverse effects of chemotherapy (I)

2. The effect of amitriptyline in treatment of chemotherapy-induced peripheral neuropathic symptoms compared with placebo (II)

3. The effect of amitriptyline in prevention of chemotherapy-induced peripheral neuropathic symptoms compared with placebo (III)

4. Two different neurotoxicity scales (the National Cancer Institute-Common Toxicity Criteria and oxaliplatin scales) in grading of chemotherapy-induced peripheral neurotoxicity (IV)

5. The changes in intraepidermal nerve fiber density during neurotoxic chemotherapy (V)
PATIENTS AND METHODS

Patients

The study included three patient populations (studies I-II, studies III-IV and study V) of cancer patients treated with neurotoxic chemotherapy at Helsinki University Hospital, Department of Oncology (studies I-IV) and Gynecology (studies III-IV) and Department of Oncology, Tampere University Hospital (study V).

Studies I-II

The screening process of the studies I and II is presented in Figure 3. Inclusion criteria were age 20 to 65 years, life expectancy of at least three months, planned duration of chemotherapy at least two months, intensity of neuropathic symptoms (numbness, tingling or pain) at least 3 measured with a numerical rating scale (0-10). Exclusion criteria were neurological disease confusing assessment of symptoms, other possible causes of neuropathy, any contraindication for amitriptyline, use of medication for neuropathic symptoms, use of medication which inhibits noradrenalin reuptake, pregnancy and lactation. Patient recruitment for the study II was terminated earlier as planned due to low recruitment rate. With permission of the Ethics Committee of the Helsinki University Central Hospital the sample size was reduced to 45. Eventually, 44 patients with advanced cancer were randomly allocated into the study, 22 subjects in both groups. This 8-week double-blind, randomized, placebo-controlled parallel group study was performed between January 2002 and August 2004.

Studies III-IV

Inclusion criteria were age 18 to 75 years, life expectancy of at least three months, planned duration of chemotherapy at least two months and absence of previous neuropathy. Exclusion criteria were the same as for the study II. For the study III, 123 consecutive patients without previous neuropathy, who started their first neurotoxic chemotherapy with vinca alcaloids, platinum derivatives, taxanes or a combination of several neurotoxic agents,
were randomized. Of them, 24 patients were excluded from the final analyses (5 due to disease confusing the assessment of neuropathic symptoms, 4 because of multiple lines of chemotherapy and 15 because of not returning the diaries). Hence, 99 patients were included in the final analyses. The study was performed between February 2003 and May 2006.
Figure 3. The screening process of the studies I and II.
<table>
<thead>
<tr>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Final Population N=152</td>
<td>Final Population N=33</td>
</tr>
<tr>
<td>NPS present</td>
<td>N=90</td>
<td>NPS absent</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>55 (31-70)</td>
<td>52 (37-67)</td>
</tr>
<tr>
<td>Gender, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (26)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Female</td>
<td>67 (74)</td>
<td>14 (82)</td>
</tr>
<tr>
<td>Diagnosis N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>46 (51)</td>
<td>10 (59)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>18 (20)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>17 (19)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other malignancies *</td>
<td>3 (3)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Chemotherapy agent N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinca-alkaloids</td>
<td>42 (47)</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Platinum derivatives</td>
<td>23 (25)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>25 (28)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Combination</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Current chemotherapy N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>23 (26)</td>
<td>0</td>
</tr>
<tr>
<td>First-line</td>
<td>34 (38)</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Second-line</td>
<td>33 (36)</td>
<td>24 (39)</td>
</tr>
<tr>
<td>Third-line</td>
<td>0</td>
<td>21 (34)</td>
</tr>
<tr>
<td>Fourth-line</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NPS, neuropathic symptoms
*only in study I

Table 4. Clinical characteristic of the patients in studies I-III.
Study V

The study population consisted of 12 cancer patients aged from 18 to 70 years and starting their first adjuvant chemotherapy with platinum derivatives or taxanes. The same exclusion criteria were applied as in the studies II and III.

Methods

Assessment of neuropathic symptoms

A questionnaire of neuropathic symptoms was used in the screening for the studies I and II. It included questions about presence of numbness, tingling, pain or impaired sensory function in hands and/or feet, clumsiness in fingers, peripheral muscular weakness or difficulties in walking, and the patients replied with yes/no answers.

In the studies II and III the intensity of the neuropathic symptoms and the global disturbance of them during the treatment were assessed with a VAS scale (0–100 mm) using a diary. It was filled twice a week during the whole study period.

The severity of sensory and motor neuropathy was graded according to the NCI-CTC scale (studies II, III and IV) and the oxaliplatin scale (studies III and IV).

Assessment of global improvement

In the study II, the patients assessed global improvement of the neuropathic symptoms with a VAS scale (0–100 mm) in the diary twice a week during the whole study period. In addition, on the final visit, they assessed the global improvement of the neuropathic symptoms using a 5-point VRS (complete relief, moderate relief, some relief, no change, worse symptoms).

Assessment of chemotherapy-induced toxicity other than neurotoxicity

Other adverse effects of chemotherapy but neuropathy were assessed by the NCI-CTC scale (studies II, III and IV) and a questionnaire including the most common chemotherapy
adverse effects (fatigue, nausea and vomiting, constipation, sweating, odema, alopecia, mucositis, eye symptoms, changes of taste and an open question of any other possible chemotherapy-related symptom) (studies I, II and III). Patients were asked to name the most troublesome chemotherapy-induced symptom (study I).

Physical examination

Neurological examination was performed by the study physician at every visit (studies I, II, III and V). The neurological examination included motor assessment (muscle strength in the limbs), sensory testing (examination of touch, pinprick, cold, warm, vibration and position sense and testing of allodynia for dynamic and static mechanical stimuli), testing of balance, co-ordination, fine motoric performance and deep tendon reflexes.

Blood samples and electrocardiogram

Blood samples (serum creatinine, transaminases, glucose, free T4, TSH and vitamin B₁₂) were taken to exclude other causes of neuropathy in the studies II, III and V. Electrocardiogram was taken to exclude cardiac contraindications to amitriptyline in the studies II and III. A blood sample for analysis of the concentration of amitriptyline was taken at 8 weeks’ visit in the studies II and III.

Randomization and blinding

In the studies II and III a computer generated randomization schedule was used to allocate the patients to either the amitriptyline or the placebo group by the hospital pharmacy. In the studies II and III the randomization was stratified according to the chemotherapy group and the diagnosis. Both patients and clinicians were blinded during the whole treatment period.

Study medication

The hospital pharmacy provided identical capsules of either placebo or amitriptyline.
In the study II the treatment was started with one 10mg drug capsule or placebo at bedtime. Dose elevation was 10 mg per week up to the target maximum dose of 50 mg/day if tolerated. In case of intolerable adverse effects dose escalation was terminated and the dose was reduced by 10 to 25 mg, if necessary. The total treatment time was 8 weeks.

In the study III the treatment was started with one 25 mg drug capsule or placebo at bedtime. Dose elevation was 25 mg per week up to the target maximum dose of 100 mg/day if tolerated. In the case of intolerable adverse effects, dose escalation was terminated and the dose was reduced by 25 mg, if necessary. The treatment was continued until the end of the neurotoxic chemotherapy.

Assessment of quality of life and depression

QoL was assessed with the EORTC-C30 questionnaire for cancer patients in the studies II and III. Depression was evaluated using the emotional functioning subscore of the EORTC-C30.

Assessment of activity of daily living, physical activity and sleep

ADL was assessed at every visit with a 6-item questionnaire including questions about eating, clothing, washing, brushing the teeth, shaving and combing the hair. Physical activity was inquired at every visit with a 4-item questionnaire including questions about physical performance, physical activity, house keeping and hobbies. These questionnaires used grading to normal, mildly impaired and severely impaired. The assessment of sleep included questions about the duration of sleep and the number of awakenings. These questionnaires were used in the studies II and III.

Assessment of side-effects of the study medication

The side effects of the study medication were queried in the diary with an open question, and the intensity of them was scored with a five-point verbal scale (none, mild, moderate, severe, untolerable) in the studies II and III.
Skin biopsy

In the study V, skin biopsies (diameter 3 mm) were taken at every study visit from the right distal leg 10 cm above the lateral malleolus. Specimens were fixed in 10% formalin and then embedded in paraffin. Ten-μm sections were immunostained with a polyclonal panaxonal marker PGP 9.5. The number of IENF was counted with a light microscope at 400 x magnification blinded to the clinical status of the patients. Three adjacent skin sections were analyzed to get proper estimation of IENF count. For the estimation of epidermal area the point-counting was performed using square lattice. The normal value for IENF density was considered as more than 40 fibres per mm² (Koskinen et al. 2005).
Table 5. Methods.

<table>
<thead>
<tr>
<th>Study</th>
<th>Neuropathic symptoms</th>
<th>Grading of neuropathic symptoms</th>
<th>Global improvement of neuropathic symptoms</th>
<th>Clinical examination</th>
<th>ADL, physical activity, sleep</th>
<th>QoL</th>
<th>Chemotherapy toxicity</th>
<th>Side effects of the study medication</th>
<th>Laboratory tests</th>
<th>Statistical analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Screening questionnaire, VAS</td>
<td>NCI-CTC</td>
<td>VAS (diary)</td>
<td>At the screening visit #</td>
<td>Questionnaire</td>
<td>EORTC-C30</td>
<td>Questionnaire</td>
<td>Questionnaire</td>
<td>Study I</td>
<td>Statistical analyses</td>
</tr>
<tr>
<td>II</td>
<td>VAS (diary)</td>
<td>NCI-CTC</td>
<td>VAS (diary)</td>
<td>At every study visit</td>
<td>Questionnaire</td>
<td>EORTC-C30</td>
<td>Questionnaire</td>
<td>Questionnaire</td>
<td>Study I</td>
<td>Statistical analyses</td>
</tr>
<tr>
<td>III</td>
<td>Global improvement</td>
<td>Oxaliplatin scale</td>
<td>History of symptoms at every study visit</td>
<td>At every study visit</td>
<td>Questionnaire</td>
<td>EORTC-C30</td>
<td>Questionnaire</td>
<td>Questionnaire</td>
<td>Study I</td>
<td>Statistical analyses</td>
</tr>
<tr>
<td>IV</td>
<td>Oxaliplatin scale</td>
<td>NCI-CTC</td>
<td>History of symptoms at every study visit</td>
<td>At every study visit</td>
<td>Questionnaire</td>
<td>EORTC-C30</td>
<td>Questionnaire</td>
<td>Questionnaire</td>
<td>Study I</td>
<td>Statistical analyses</td>
</tr>
<tr>
<td>V</td>
<td>History of symptoms at every study visit</td>
<td>NCI-CTC Oxaliplatin scale</td>
<td>History of symptoms at every study visit</td>
<td>At every study visit</td>
<td>Questionnaire</td>
<td>EORTC-C30</td>
<td>Questionnaire</td>
<td>Questionnaire</td>
<td>Study I</td>
<td>Statistical analyses</td>
</tr>
</tbody>
</table>

# for symptomatic patients only
* results not reported

**Statistical analyses**

Statistical analyses were performed using SPSS 12.0 for Windows.

**Study I**

Clinical characteristics of the two groups (patients with and without neuropathic symptoms) were compared using t-test or chi-square test. The occurrence of chemotherapy-induced symptoms and the most troublesome symptom in the two groups were analysed using age- and sex-adjusted logistic regression models. No adjustment was made for multiple testing.
but this information can be obtained by multiplying the actual p-value by the number of comparison made.

Study II

Global improvement, severity of neuropathic symptoms, QoL, depression and anxiety were tested by repeated-measures analysis of variance (ANOVA model) with treatment group as grouping variable. Between and within groups comparisons were performed with T-test. The planned study size was 120 patients. With permission of the Ethics Committee of the Helsinki University Central Hospital the sample size was later resized to 45 with a significance level of 0.05 and power of 0.80 to identify a 30 % difference between the groups.

Study III

Analyses were performed on the intent-to-treat population, defined as all randomized patients who returned their diaries at the follow-up visits. The last-observation-carried-forward approach was used for missing data. Statistical comparison between groups was made by using either t-test or chi-square test. The appearance and progression of neuropathic symptoms was assessed with neuropathy score: the sum of the intensity of the different symptoms (no=0, mild=1, moderate=2, severe=3) divided by ten, the score having a theoretical range from 0 (no symptoms) to 3 (all ten symptoms graded as severe). The area under the curve for neuropathy score was calculated with the trapezoidal method. Permutation test was used to test differences between groups for side effects and bootstrap-based multiplicity adjustment was applied to correct levels of significance for multiple testing. QoL data were analyzed using generalizing estimating equations models with the exchangeable correlation structure. Correlation coefficients were calculated by the Spearman method.

The planned study size was 250 patients. This study was designed to have 125 patients in each arm to provide 80 % power (α error, 0.05) to detect a 20 % change in symptom score, which was regarded as a clinically significant change. According to the original protocol, interim analyses were carried out when 120 patients had been randomized. Because of the
negative results in the interim analyses, recruitment was cancelled after 123 patients had been randomized.

**Study IV and V**

These studies were descriptive. No statistical comparisons were made.

**Ethical considerations**

The studies were approved by the Ethics Committee of the Helsinki University Central Hospital (studies I-IV) and Tampere University Hospital (V), and a written informed consent was obtained from all participants.
RESULTS

Burden of CIPN (study I)

At the screening visit, 90 out of 152 (59 %) patients who were treated with neurotoxic chemotherapy reported neuropathic symptoms. Tingling (71 %), numbness (58 %), impaired sensory function (46 %) and pain in hands and feet (40 %) were the most common symptoms. The median intensity of neuropathic symptoms was 28/100 on the visual analogue scale (0-100). Grading has been reported in Table 6.

Table 6. Grading of neuropathic sensory symptoms by NCI-CTC in the screening and prevention populations (studies I and III)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Screening (152 patients) % of patients</th>
<th>Prevention study visit 2 (97 patients) % of patients</th>
<th>Prevention study visit 3 (79 patients) % of patients</th>
<th>Prevention study visit 4 (41 patients) % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>41 %</td>
<td>39 %</td>
<td>44 %</td>
<td>24 %</td>
</tr>
<tr>
<td>1</td>
<td>13 %</td>
<td>56 %</td>
<td>35 %</td>
<td>39 %</td>
</tr>
<tr>
<td>2</td>
<td>25 %</td>
<td>3 %</td>
<td>18 %</td>
<td>20 %</td>
</tr>
<tr>
<td>3</td>
<td>22 %</td>
<td>2 %</td>
<td>3 %</td>
<td>17 %</td>
</tr>
<tr>
<td>4</td>
<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>

In the whole cohort of 152 patients, fatigue (66 %), mucositis (61 %) and neuropathic symptoms (59 %) were the most commonly reported symptoms. In addition, every third patient (37 %) with neuropathic symptoms ranked them as the most troublesome symptom.
Amitriptyline in prevention and treatment of CIPN (studies II, III)

Tolerability of amitriptyline

Amitriptyline was well tolerated both in the prevention and treatment studies (II, III). In the treatment study (II) 15 patients out of 17 (88 %) reached the target dose and completed the study. The daily dose was reduced from 30 to 10 mg in one patient because of tiredness (6 %) and from 50 to 25 mg in another patient because of tachycardia (6 %). After the dose reduction, the adverse effect disappeared but the neuropathic symptoms exacerbated in both patients. There was no significant association between the severity of the side effects and the drug concentration (study II). In the placebo group three patients terminated the study during the dose titration due to side-effects (16 %).

In the prevention study (III) 40 out of 54 patients (74 %) with amitriptyline reached the target dose (100 mg). The dose was reduced to 25 mg in one patient and to 50 mg in 13 patients. The most common reason for dose reduction was tiredness (n=11, 20.4 %). Dry mouth (2 %), visual disturbances (2 %) and constipation (2 %) caused dose reduction in one patient each. In the placebo group the dose was reduced to 50 mg in 4 patients out of 45 because of palpitation (2 %), dizziness (2 %), dry mouth (2 %) and tiredness (2 %) in one patient each. Dry mouth was more severe in the amitriptyline group both at the dose titration phase (p<0.001) and stable dose phase (p<0.001). Tremor was more severe in the amitriptyline group at the stable dose phase (p=0.034).

Prevention of CIPN (study III)

The intensity of neuropathy was mild in general (Figure 4b). There was no significant difference between the amitriptyline and placebo groups in the intensity of the neuropathic symptoms (Figure 4a).
In line with results of the neuropathic score, there was no significant difference in NCI-CTC scoring between the amitriptyline and placebo groups. After 3, 6 and 9 chemotherapy cycles, sensory neuropathy was seen in 61% of the patients (57% in the amitriptyline group and 65% in the control group), 56% (56% and 56%) and 76% (67% and 85%), respectively, and motor neuropathy in 26% (22% and 30%), 36% (32% and 42%) and 22% (14% and 30%). Neuropathy was mild, grade 1, in the majority of the cases. (Table 6).

**Treatment of CIPN (study II)**

There was a trend towards better global improvement of the neuropathic symptoms with amitriptyline assessed by the patients using VAS: after eight weeks, the mean VAS (± SD) for global improvement was 3.4 ± 3.6 in the amitriptyline group and 1.9 ± 3.1 in the placebo group, respectively. Global improvement measured by VRS demonstrated at least some relief
of neuropathic symptoms in eight (47 %) and five (31 %) patients in the amitriptyline and placebo groups, respectively, however, these differences were not statistically significant.

There was no statistically significant difference in the severity of the neuropathic symptoms between the amitriptyline and placebo groups during the study. The disturbance of all neuropathic symptoms was, in general, low: varying from 0 to 8.2 (mean 2.5) at baseline. Paresthesia and tingling were the most common symptoms, reported by 25 out of 33 (76 %) patients. Pain was present in 19 (58 %) and itching in 15 (45 %) patients.

According to the NCI-CTC scale, Grade I-II sensory neuropathy was found in 31 (70 %) patients and Grade I-II motor neuropathy in 21 (64 %) patients. No Grade 3 or 4 neuropathy was seen.

Amitriptyline improved QoL measured with the EORTC QLQ-C30 (global health score) statistically significantly compared with placebo ($P = 0.038$). The improvement of QoL was not related to either depression or sleep. The mean global health scores for the amitriptyline and placebo treated patients were 48 and 62 at baseline, 62 and 54 after 4 weeks, and 55 and 49 after 8 weeks, respectively.
Assessment (study IV)

The NCI-CTC sensory and the oxaliplatin scales were comparable in identifying neuropathic symptoms. The oxaliplatin score was more sensitive at detecting changes in the progression of the neuropathic symptoms compared with the NCI-CTC scale. The progression of the toxicity from mild (grade 1-2) to moderate or severe (grade 3-4) was detected more frequently with the oxaliplatin scale.

Of the patients with grade 3-4 toxicity by the oxaliplatin scale, 23/53 had grade 1 toxicity by the NCI-CTC scale, 18/53 had grade 2 and 12/53 had grade 3 neurotoxicity. However, the oxaliplatin scale was in line with the NCI-CTC scale in 12/13 patients with grade 3 symptoms.

Intraepidermal nerve fiber density (study V)

Reduced IENF density was found in 8 patients out of 12 at baseline and all of them had normal sensory findings in clinical examination. During the follow-up, the IENF density increased significantly in six of them and remained unchanged in two. In four patients the IENF density was normal both at baseline and at the end of the follow-up period. Neuropathic symptoms were manifested in nine patients, but no association with the IENF count was found.
DISCUSSION

Prevalence and burden of chemotherapy-induced neuropathy

The prevalence of neuropathic symptoms varied depending on the chemotherapeutic agents, treatment schedule, cumulative doses and study population. Symptoms were most common in patients treated with vincristine (70 %), oxaliplatin (70 %) and paclitaxel (70 %). Patients with and without neuropathic symptoms differed from each other by age ($p=0.004$).

Longitudinal follow up studies of the symptoms are lacking. The prevalence of neuropathic symptoms (59 %) in the present cross-sectional study was, however, in line with previous literature (Argyriou et al, 2011). In the present population neuropathic symptoms was the third most common adverse effect of chemotherapy, when neurotoxic agents were used.

In the current study, albeit the neuropathic symptoms were common, their intensity was mild. However, despite the low intensity, every third patient rated neuropathy, when present, as the most troublesome symptom. This discrepancy could be related, at least partly, to difficulty to score neuropathic symptoms other than pain. VAS is well documented in the measurement of the intensity of neuropathic pain in diabetes and PHN. In CIPN, however, tingling and numbness are the most common symptoms (Wolf et al, 2008). Similarly, in the present study tingling and numbness were experienced approximately by two thirds of the patients (71 and 58 %, respectively), while pain was only the fourth commonest symptom reported by 40 % of the patients. VAS has not been widely used to measure the intensity of CIPN symptoms so far. In a recent lonigitudinal study using VAS to assess CIPN, VAS was found to be able to recognize difference between two neurotoxic treatment regimens and catch the change in peripheral neuropathic symptoms. Interestingly, the authors noticed that pain and numbness had separate patterns of appearance (Takemoto et al, 2011). Another plausible explanation for the discrepancy between the intensity and inconvenience is the chronic character of neuropathic symptoms, which can cause discomfort in daily life even when it is mild and does not interfere with function, like tingling and numbness. The difference in the sensory and affective dimensions of pain and other sensory symptoms may also influence the result (Haanpää et al, 2011), but as we did not use McGill pain questionnaire which is able to capture this we cannot analyze this hypothesis. The finding in the present study of the low intensity but high inconvenience caused by neuropathic symptoms highlights the importance of careful measurement of neuropathic symptoms. This is important as more cancer patients are exposed to neurotoxic agents.
Assessment of chemotherapy-induced neuropathy

The analysis of the prevalence and severity of neuropathic symptoms caused by chemotherapy is challenging as the patients often receive different types of chemotherapeutic agents at different doses and for various cancers. Patients with advanced cancer and numerous chemotherapy treatments have many other disturbing symptoms, such as cancer-related pain, nausea, and fatigue, which also attract their attention and may cause underrating of the severity of neuropathic symptoms. In addition, some patients may be unwilling to report neuropathic symptoms that might lead to the cessation of chemotherapy. The intensity of the symptom does not necessarily correlate to functional impairment, like capability to button a shirt. These features of patients with chemotherapy-induced neuropathy make the comparison of neuropathic symptoms caused by chemotherapy and other diseases, such as diabetes or herpes zoster, problematic.

To date, there is no agreement on the best way to assess the severity of CIPN. The method should include assessment of symptoms, signs, functional ability and electrophysiological findings. In clinical practice, assessment including symptoms and physical examination is probably the most sensitive and reliable method of detecting CIPN because of lack of reliable objective methods suitable for clinical use (Velasco and Bruna, 2010; Kaley and Deangelis, 2009; Ocean, 2004; Cavaletti, 2011). Especially symptoms (clumsiness of the hands or numbness or pain in the feet) and signs that influence daily living and QoL are important. Careful instrumental technical methods are often available but they are time-consuming and not always feasible in the clinic. They provide a quantitative estimate of severity, but their principal role is in research (Velasco and Bruna, 2010; Cavaletti et al, 2011).

The role of patient-reported outcomes is increasing (Garcia et al, 2007). In chronic pain and other troublesome symptoms, where the importance of a subjective symptom must be considered against the background of the patient’s subjective values, patient-reported outcome measures have particular weight. In clinical practice and also clinical research the role of history of symptoms and their impact is hence crucial. Recently (after our study was commenced) many patient-based assessment instruments such as the Functional Assessment of Cancer Therapy/Cynecologic Oncology Group-Neurotoxicity (Huang et al, 2007), the QLQ-CIPN20 of the EORTC (Postma et al, 2005) and the Patient Neurotoxicity Questionnaire (Shimozuma et al, 2009) have been published. However, the disadvantage of these patient-based instruments seems to be that they are somewhat cumbersome to administer (Takemoto et al, 2011). A recent systematic review concluded than currently
there is little evidence to support for the hypothesis that disease-, symptom- or treatment-specific instruments are more sensitive and responsive than cancer-specific or generic questionnaires. However, the conclusions were limited by the small number of head-to-head comparisons available (Luckett et al, 2010).

Grading of CIPN

The NCI-CTC scale is the most commonly used scale in rating neurotoxicity in oncology (Argyriou et al, 2011; Carlson and Ocean, 2011). Scoring neurotoxicity by NCI-CTC is based on whether the symptom interferes with function (grade 2), with ADL (grade 3), or whether the symptom permanently interferes with function or causes paralysis (grade 4). Grades 3 and 4 represent severe symptoms and are commonly reported in chemotherapy trials. For oxaliplatin neurotoxicity, a special grading system for the assessment of oxaliplatin-induced paraesthesia/dysaesthesia by Levi (Lévi et al, 1992) has been conducted (Cavaletti et al, 2010). On the contrary to NCI-CTC scale the oxaliplatin scale is based on the duration of the symptoms. Toxicity that does not disappear between the chemotherapy cycles is classified as severe (grade 3). On both scales grade 4 toxicity includes permanent symptoms with interference with function or ADL. There is, however, no consensus as to which factors, the degree of functional impairment, or the continuity of the symptoms that are the most important in determining the clinical severity of neuropathy. The reversibility of long-lasting grade 3 neurotoxicity by oxaliplatin scale has been 74 % with a median time to recovery within 13 weeks (de Gramont et al, 2000; Land et al, 2007). However, even after 18 months of oxaliplatin-based chemotherapy 22 % of the patients reported numbness and tingling in the feet, and after two years over 10 % of the patients still reported symptoms (Land et al, 2007). Such information is lacking from NCI-CTC-scale.

Park et al. compared the NCI-CTC and oxaliplatin scale in patients who were treated with oxalipatin (Park et al, 2011). By completion of the treatment, 20 % of the patients had severe chronic neuropathy (NCI-CTC grade 3), 51 % moderate (NCI-CTC grade 2) and 29 % mild neurotoxicity (NCI-CTC grade 1). They found that the oxaliplatin scale demonstrated the same distribution of grades of neurotoxicity severity as the NCI-CTC scale.

Likewise in the present population of chemotherapy-naïve patients who started neurotoxic chemotherapy including also other neurotoxic drugs than oxaliplatin, the scales were equally sensitive in detecting early neurotoxicity. However, there was a noticeable difference between the scales in detecting the progression of neurotoxicity. The NCI-CTC sensory
scale classified neurotoxicity more often as mild (grade 1 to 2) while the oxaliplatin scale showed incomplete regression of the symptom (grade 3 to 4). One plausible explanation for this is the subjectivity of the NCI-CTC grading. In particular, the difference between grade 2 (interference of symptoms with function) and grade 3 (interference of symptoms with activity of daily living) is not entirely objective. For example, clumsiness of hands does interfere with function, but the interference with activity of daily living varies individually, depending on patients’ age, performance status, profession, family, housing and leisure time activities. In addition, patients may under estimate or, on purpose, under-report the discomfort of the toxicity because they are worried of the future treatment options. This may explain, at least partly, the lower rate of grade 3 neurotoxicity by the NCI-CTC. On the other hand, the oxaliplatin scale is more objective as the grading is based on duration and continuity of the symptoms. Thus, in the present population, the duration of the symptoms appears to be more sensitive than the functional impairment reported by the patients in detection of progression of neurotoxicity. The fact that the oxaliplatin scale more sensitively detected the progression of neurotoxicity could be significant because early progression of neuropathic symptoms might reflect more severe toxicity later in the chemotherapy course or neuropathic pain later in life.

Similarly to the NCI-CTC sensory grading, the motor grading is subjective, too. Muscular weakness is a common symptom of cancer patients especially in elderly patients, in metastatic cancer and during corticosteroid medication. For that reason, identification of neuropathy-related muscular weakness is challenging. In the present study, every third to fourth patient reported motor symptoms, but they were no more than mild (only grade 1), without any objective findings. This is in line with earlier reports (Park et al, 2011). Thus, the prognostic significance of these findings is questionable.

**Intraepithelial nerve fibers**

The principal finding of the IENF (V) study was that IENF densities can be noticeably reduced in cancer patients, even prior to starting adjuvant chemotherapy implying that neurotoxic chemotherapeutic agents can not be solely blamed for neuropathy. Some patients could develop paraneoplastic small fibre neuropathy, which may be subclinical at first, but it may amplify the impact of neurotoxicity of chemotherapy (Lipton et al, 1991) were first to demonstrate a subclinical small fibre dysfunction in cancer patients untreated with chemotherapeutic agents. In line with our findings, they found that 50 % of cancer patients had elevated thermal thresholds.
Contrary to our preliminary hypothesis, neurotoxic chemotherapy does not always induce loss of IENFs. Also the normalization of fibre count may happen during the chemotherapy. Burakgazi et al (Burakgazi et al, 2011) reported a significant reduction in IENF density in patients receiving oxaliplatin with similar different evolutional patterns as in some patients of our study. However, we did not found any association between the IENF count and neurological symptoms, which can be, at least partly, due to small number of patients and many different patterns in evolution of IENF counts in the present study. The results of this pilot study need to be confirmed in a larger patient population with longer follow-up and combined IENF and QST.

**Prevention of CIPN**

The present study is the first prospective randomized controlled study of the efficacy of amitriptyline, one of the most potent treatments of peripheral neuropathy with various ethiologies, e.g., diabetic neuropathy, PHN and postsurgical neuropathic pain (Kalso et al, 1996; Saarto and Wiffen 2010) in prevention of CIPN. In line with the previous prevention studies with other agents, the present study failed to demonstrate any effect of amitriptyline in prevention of CIPN. However, we can’t rule out a small difference (below 30 %) between the study groups because of the small size of this study. In our study, the daily dose of amitriptyline was up to 100 mg, which is in line with the studies on painful neuropathy (Wolf et al, 2008). Amitriptyline has been shown to prevent post-herpetic neuralgia even at a low dose of 25 mg daily (Bowsher, 1997). However, the intensity of neuropathic symptoms in the present study was rather low, which could have diluted the effect. Interestingly, anticonvulsants, like gabapentin and carbamazepine have also failed to show any efficacy over placebo in prevention of CIPN (Mitchell et al, 2006; von Delius et al, 2007). The results of some other drugs tested in the prevention of chemotherapy-induced neuropathy such as amifostine, diethylthiocarbamate, glutathione, leukaemia inhibitory factor, N-acetylcysteine, nimodipine, hexapeptide analogue Org 2766, and vitamin E have also been inconsistent (Wolf et al, 2008). As yet, no neuroprotective drugs are recommended for routine use to prevent CIPN in clinical practice.
Treatment of CIPN

TCAs together with anticonvulsants are the first-line and most effective drugs for neuropathic pain (Saarto and Wiffen 2010; Bril et al., 2011). The present study (II) was the first prospective, randomized, controlled study of the efficacy of amitriptyline in treatment of CIPN symptoms.

In our study amitriptyline did not, however, improve sensory neuropathic symptoms even though there was a trend towards global improvement in favour of the amitriptyline group. The study was premature interrupted because of the low recruitment rate with statical power of finding the 30 % difference between the study groups. A relatively low dose (50mg/day) of amitriptyline was chosen to avoid adverse events and increase compliance. However, amitriptyline has been demonstrated to be effective in relieving postoperative neuropathic pain in women with breast cancer already in doses of 25-50 mg/day (Kalso et al., 1996). In line with the present study, another small study of nortriptylin in cisplatin-induced painful neuropathy also failed to demonstrate any significant improvement in neuropathic symptoms. Duloxetine has impaired oxaliplatin-induced neuropathy in an open-label study. However, it has many adverse effects and interactions with other drugs like tamoxifen (Yang et al., 2011).

Two clinical studies of gabapentin on chemotherapy-induced neuropathic symptoms have also been published (Bosnjak et al., 2002; Rao et al., 2007). A small uncontrolled study reported promising results with a 900 mg daily dose of gabapentin (Bosnjak et al., 2002), but a placebo controlled prospective randomised study with 115 patients failed to alleviate pain intensity or sensory neuropathic symptoms with 2700 mg of gabapentin (Wong et al., 2005). So far, no treatment is available for clinical use in treatment of chemotherapy-induced neuropathy.

Challenges in prevention and treatment of CIPN

CIPN is an important adverse effect as it may limit the dose of the anti-cancer treatment and reduce the QoL of cancer patients and survivors. Neuroprotective therapies have been sought for coadministration of chemoprotective or rescue therapies to reduce adverse effects without reversing anti-tumor activity. Various agents have been tried in clinical and experimental models to prevent CIPN, but, so far, no treatment is available for clinical use in
prevention of CIPN due to inefficiency or safety problems (Argyriou et al, 2011). One of the most promising neuroprotective treatments have been Ca/Mg infusions. In a retrospective study, Ca/Mg infusions before and after oxaliplatin treatment reduced the incidence of acute neurologic symptoms, and the oxaliplatin therapy was less frequently discontinued due to neurotoxicity among patients who were pretreated with Ca/Mg infusion (Gamelin et al, 2004). However, in the prospective study there was alerting findings of a significantly lower tumor response rate in the group receiving calcium/magnesium infusions and the study was closed prematurely (Hochster et al, 2007).

The mechanism behind CIPN is not fully understood. Although TCAs and anticonvulsants are effective treatments of painful diabetic neuropathy and PHN, their efficacy in CIPN has not been proven yet. Interestingly, also in HIV related neuropathy TCAs (Kieburtz et al, 1998; Shlay et al, 1998) and gabapentin (Hahn et al, 2004) have failed to improve neuropathic symptoms. Lamotrigine showed statistically significant pain relief in a small randomised controlled trial of painful HIV neuropathy (Simpson et al 2000), but in a larger randomised controlled trial the efficacy was shown only in those patients who had received neurotoxic antiretroviral therapy (Simpson et al, 2003).

Neuropathies of different causes seem to respond differently to therapies that may reflect differences in the mechanisms of neuropathies from various aetiologies. Another plausible explanation could be the different symptom profile. The most prominent symptoms of chemotherapy-induced neuropathy are paraesthesia, dysesthesia and numbness, which may be less responsive to pharmacotherapy than neuropathic pain dominating in other neuropathies.

Despite the lack of significant improvement in neuropathic symptoms, amitriptyline significantly improved QoL of patients with advanced cancer. Amitriptyline was also well tolerated. None of the patients quitted amitriptyline treatment because of side effects. Thus, in selected patients with advanced disease, low dose amitriptyline could be still beneficial.
SUMMARY AND CONCLUSIONS

Chemotherapy-induced neuropathy is a common adverse effect. Approximately two thirds of the patients treated with neurotoxic chemotherapy reported neuropathic symptoms. In the present study the intensity of neuropathic symptoms was relatively low. However, the intensity and inconvenience of the neuropathic symptoms do not correlate with each other. Neuropathic symptoms seem to be very troublesome despite of the low intensity.

There are many tools to assess neuropathic symptoms. In oncology the NCI-CTC scale is used most widely. The oxaliplatin neurotoxicity scale has been used only in grading neurotoxicity induced by oxaliplatin so far. We compared the above mentioned scales in grading CIPN. Both scales were equally sensitive in detecting early CIPN in patients treated with neurotoxic chemotherapy agents other than oxaliplatin. However, the oxaliplatin scale was more sensitive in showing progression in the form of the duration of the symptoms. The fact that the oxaliplatin scale more sensitively detected the progression of neurotoxicity could be important, because early progression of neuropathic symptoms might reflect more severe toxicity later in the chemotherapy course or neuropathic pain later in life. Hence, oxaliplatin scale seems to be useful in grading CIPN not only in patients treated with oxaliplatin but also those treated with other neurotoxic agents. It’s advantage is that it takes into account the duration of symptoms.

Despite the fact that TCAs and anticonvulsants are the most effective drugs in treatment of painful peripheral neuropathies, they have not been effective in the treatment or prevention of CIPN. In the present studies amitriptyline failed to prevent or treat CIPN. Thus, there is no effective treatment option for prevention or treatment of CIPN so far. However, despite the lack of significant effect of amitriptyline in treatment of CIPN, in treatment of patients with advanced cancer, amitriptyline may improve QoL.

IENF density can be markedly reduced in cancer patients, even prior to starting adjuvant chemotherapy, which could partly influence the development of commonly encountered abnormalities in sensation and neuropathic pain during chemotherapy.

In summary, CIPN is a common adverse effect of neurotoxic chemotherapy regimens. Despite being often rather mild, it causes considerable discomfort to patients due to its often chronic character. There is no standard global method for either assessment, prevention or treatment of CIPN, other than limitation of the total dose or changing the treatment schedule of neurotoxic agents.
1. Chemotherapy-induced neuropathy is a common adverse effect with low intensity. However, the intensity and inconvenience of the neuropathic symptoms do not correlate with each other. Neuropathic symptoms seem to be very troublesome even though the intensity of the symptoms is generally mild.

2. The NCI-CTC sensory scale and the oxaliplatin scale are equally sensitive in detecting early CIPN in patients treated with neurotoxic chemotherapeutic agents, also other than oxaliplatin. However, the oxaliplatin scale is more sensitive in showing progression in the form of the duration of the symptoms. Hence, it seems to be useful in grading CIPN both in patients treated with oxaliplatin and in those treated with other neurotoxic agents.

3. Amitriptyline does not seem to prevent chemotherapy neurotoxicity.

4. Amitriptyline improves QoL of cancer patients even though it does not significantly improve symptoms of CIPN.

5. Density of IENF can be markedly reduced in cancer patients, even prior to starting adjuvant chemotherapy, but the changes in the IENF density are not associated with clinical symptoms of neuropathy.
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