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# Predictors of Chemotherapy-Induced Peripheral Neuropathy

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## 1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting toxicity of chemotherapy that often develops in response to administration of various drugs, including, molecularly targeted therapeutic agents (bortezomib), taxanes (paclitaxel, docetaxel), platinum compounds, platinum-containing drugs (cisplatin, carboplatin, oxaliplatin), vinca alkaloids (vincristine), thalidomide, lenalidomide, and epothilones (ixabepilone) (Kannarkat et al., 2007; Ocean et al., 2004; Park et al.,2008; Walker et al., 2007; Windebank et al., 2008; Wolf et al., 2008). It has been postulated that CIPN may represent the initial stage in the development of neuropathic pain. Although the symptoms of CIPN are diverse, the condition consistently reduces patient quality of life (QOL). Unfortunately, effective strategies for preventing or treating CIPN remain elusive.

To identify significant predictors for CIPN which would contribute to improving QOL among chemotherapy patients, we conducted a study, entitled, "Statistical identification of predictors for peripheral neuropathy associated with administration of bortezomib, taxanes, oxaliplatin or vincristine using ordered logistic regression analysis" (Kanbayashi et al., 2010). In this review, we will discuss the predictors for CIPN and review other studies.

## 2. Predictors of CIPN

CIPN is a dose-limiting toxicity of chemotherapy that often develops in response to administration of various drugs, in particular, bortezomib, taxanes (paclitaxel, docetaxel), oxaliplatin and vincristine (Kannarkat et al., 2007; Ocean et al., 2004; Park et al.,2008; Walker et al., 2007; Windebank et al., 2008; Wolf et al., 2008). However, effective strategies for preventing or treating CIPN are lacking. Accordingly, we conducted a retrospective study to identify significant predictors for CIPN which would contribute to improving QOL among chemotherapy patients (Kanbayashi et al., 2010). Patients had been administered bortezomib (n=28), taxanes (paclitaxel or docetaxel; n=58), oxaliplatin (n=52) or vincristine (n=52) at our hospital between April 2005 and December 2008.

| | Bortezomib (*N*=28) | Taxanes (*N*=58) | Oxaliplatin (*N*=52) | VCR (*N*=52) |
|---|---|---|---|---|
| *Demographic* | | | | |
| Sex (male), *N* (%) | 16 (57.1) | 36 (62.1) | 32 (61.5) | 27 (51.9) |
| Age, Mean (SD) | 59.9 (13.9) | 65.3 (9.3) | 62.2 (12.3) | 63.8 (13.0) |
| Age ≥60 years, *N* (%) | 17 (60.7) | 40 (67.0) | 32 (61.5) | 25 (48.1) |
| *Comorbidity* | | | | |
| DM, *N* (%) | 3 (10.7) | 5 (8.6) | 6 (11.5) | 4 (7.7) |
| *Concomitant medication* | | | | |
| Opioid, *N* (%) | 5 (17.9) | 8 (13.7) | 10 (19.2) | 8 (15.4) |
| NSAIDs, *N* (%) | 8 (28.6) | 21 (36.2) | 16 (30.8) | 12 (23.1) |
| NSAIDs (COX-2), *N* (%) | - | 10 (17.2) | - | - |
| Analgesic adjuvant (%) | 17 (60.7) | - | 8 (15.4) | 10 (19.2) |
| *Concomitant use of cancer drugs* | | | | |
| DEX, *N* (%) | 13 (46.4) | - | - | 5 (9.6) |
| Thalidomide, *N* (%) | 1 (3.8) | - | - | - |
| Cisplatin, *N* (%) | - | 14 (24.1) | - | - |
| TS-1, *N* (%) | - | 12 (20.7) | - | - |
| Number of chemotherapy cycles (1), Mean (range) | 11.1±14.5 (3-75) | 6.6±7.7 (1-46) | 8.2±6.0 (1-25) | 3.8±2.9 (1-18) |
| Number of chemotherapy cycles (2) (<6/6-10/>10) | 9/14/5 | 34/17/7 | 20/19/13 | 37/15/0 |
| *Type of cancer* | | | | |
| Gastric cancer, *N* (%) | | 20 (34.5) | | |
| Esophageal cancer, *N* (%) | | 35 (60.3) | | |
| Cecal cancer, *N* (%) | | 1 (1.7) | | |
| Cholangiocarcinoma, *N* (%) | | 1(1.7) | | |
| Malignant mesothelioma, *N* (%) | | 1(1.7) | | |
| Colorectal cancer, *N* (%) | | | 52 (100) | |
| MM, *N* (%) | 28 (100) | | | 5 (9.6) |
| NHL, *N* (%) | | | | 39 (75.0) |
| Leukemia, *N* (%) | | | | 8 (15.4) |

DM, diabetes mellitus; VCR, vincristine; NSAID, non-steroidal anti-inflammatory drug; COX, cyclooxygenase; DEX, dexamethasone; TS-1, tegafur, 5-chloro-2,4-dihydroxypyridine, and oteracil potassium; MM, multiple myeloma; NHL, non-Hodgkin lymphoma

Table 1. Clinical characteristics of patients and factors potentially affecting occurrence of peripheral neuropathy.

Table 1 presents the clinical characteristics of the patients administered bortezomib, taxanes (paclitaxel or docetaxel), oxaliplatin or vincristine, as well as selected predictors (=*X:* independent variable) related to the manifestation of CIPN. The analgesic adjuvants that were co-administered consisted of anti-epileptic agents (gabapentin, clonazepam, and carbamazepine), tricyclic antidepressants (amitriptyline), mexiletine, vitamin $B_{12}$ and

Japanese herbs (Shakuyaku-Kanzo-To and Gosha-Jinki-Gan). Table 2 provides data on the severity of CIPN at the time of chemotherapy completion (=*Y:* dependent variable), graded from 0 to 5 in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (Table 3). We elucidated predictors for CIPN using ordered logistic regression analysis (Table 4). Among patients administered bortezomib, the risk of CIPN was significantly increased among males, but significantly decreased by the co-administration of dexamethasone. The number of drug administration cycles was a significant predictor of CIPN risk among patients administered taxanes, oxaliplatin, or vincristine. The risk of CIPN among patients administered oxaliplatin was decreased by the co-administration of non-steroidal anti-inflammatory drugs (NSAIDs). Finally, the co-administration of an analgesic adjuvant increased CIPN risk among patients administered vincristine. We used a statistical approach to identify predictors for CIPN. CIPN will be alleviated by coadministration of dexamethasone with bortezomib and NSAIDs with oxaliplatin. Our study has limitations in terms of the retrospective nature of the investigation and the relatively small number of patients analyzed, but the statistical identification of predictors for CIPN should contribute to the establishment of evidence-based medicine in the prophylaxis of CIPN and improving QOL for patients undergoing chemotherapy.

| | Number of patients | | | |
|---|---|---|---|---|
| CTCAE v3.0 | Bortezomib (n=28) | Taxanes (n=58) | Oxaliplatin (n=52) | Vincristine (n=52) |
| 0 | 10 | 48 | 26 | 31 |
| 1 | 5 | 2 | 8 | 3 |
| 2 | 6 | 4 | 16 | 15 |
| 3 | 7 | 4 | 2 | 3 |
| 4 | 0 | 0 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 |

Table 2. Results of sensory peripheral neuropathy assessments using CTCAE v3.0.

| | Grade | | | | | |
|---|---|---|---|---|---|---|
| Adverse event | 0 | 1 | 2 | 3 | 4 | 5 |
| Neuropathy-sensory | Normal | Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function | Sensory alteration or paresthesia (including tingling), interfering with function but not interfering with ADL | Sensory alteration or paresthesia interfering with ADL | Disabling | Death |

ADL, activities of daily living.

Table 3. National Cancer Institute Common Toxicity Criteria - version 3 (2006).

| Variable | EV | SE | $\chi^2$ value | P | OR | CI of OR | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower 95% | Upper 95% |
| Table 4-1: Bortezomib (accuracy=14/28) | | | | | | | |
| DEX | -0.809 | 0.389 | 4.32 | 0.0376* | 0.445 | 0.208 | 0.955 |
| Sex (male) | 1.110 | 0.411 | 7.30 | 0.0069* | 3.035 | 1.356 | 6.793 |
| Table 4-2: Taxanes (accuracy=49/58) | | | | | | | |
| Number of chemotherapy cycles (2) | 0.867 | 0.424 | 4.17 | 0.0412* | 2.379 | 1.035 | 5.466 |
| DM | 0.690 | 0.495 | 1.94 | 0.1632 | 1.993 | 0.756 | 5.257 |
| Table 4-3: Oxaliplatin (accuracy=34/52) | | | | | | | |
| Number of chemotherapy cycles (2) | 1.128 | 0.336 | 11.25 | 0.0008* | 3.089 | 1.598 | 5.972 |
| NSAIDs | -0.934 | 0.353 | 7.00 | 0.0082* | 0.393 | 0.197 | 0.785 |
| Table 4-4: Vincristine (accuracy=42/52) | | | | | | | |
| Age | 0.795 | 0.458 | 3.01 | 0.0828 | 2.215 | 0.902 | 5.438 |
| Number of chemotherapy cycles (2) | 1.794 | 0.593 | 9.14 | 0.0025* | 6.015 | 1.880 | 19.248 |
| Analgesic adjuvant | 1.363 | 0.530 | 6.62 | 0.0101* | 3.907 | 1.383 | 11.031 |
| NSAIDs | 0.842 | 0.460 | 3.35 | 0.0670 | 2.320 | 0.943 | 5.711 |

* $P < 0.05$

EV, estimated value; SE, standard error; CI, confidence interval; OR, odds ratio; DEX, dexamethasone; DM, diabetes mellitus; NSAIDs, non-steroidal anti-inflammatory drugs

Table 4. Results of logistic regression analysis for variables extracted by forward selection.

### 2.1 Bortezomib

Bortezomib is a dipeptide boronic acid analogue with antineoplastic activity. Bortezomib reversibly inhibits the 26S proteasome, a large protease complex that degrades ubiquinated proteins. By blocking the targeted proteolysis normally performed by the proteasome, bortezomib disrupts various cell signaling pathways, leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis. Specifically, the agent inhibits nuclear factor (NF)-kappaB, a protein that is constitutively activated in some cancers, thereby interfering with NF-kappaB-mediated cell survival, tumor growth, and angiogenesis. In vivo, bortezomib delays tumor growth and enhances the cytotoxic effects of radiation and chemotherapy (National Cancer Institute., 2011). Mitochondrial and endoplasmic reticulum damage seems to play a key role in bortezomib-induced PN genesis, since bortezomib is able to activate the mitochondrial-based apoptotic pathway (Pei et al., 2004).

Among cases complicated by diabetes mellitus (DM), the administration of thalidomide reportedly increased the risk of bortezomib-induced PN (Badros et al., 2007). Reducing the dosage of bortezomib and/or changing the treatment schedule are also reportedly effective in alleviating bortezomib-induced PN (Argyriou et al., 2008a). However, neither the number

of chemotherapy cycles nor the diagnosis of DM predicted bortezomib-induced PN (Kanbayashi et al., 2010). Additionally, since the use of thalidomide is not covered by the health insurance system in Japan, few patients (1 of 28 patients treated with bortezomib) received thalidomide co-administration (Kanbayashi et al., 2010). Thus, we did not include thalidomide in our analysis. However, we found that co-administration of dexamethasone was able to alleviate bortezomib-induced PN. A recent report found that the immune system is involved in bortezomib-induced PN (Ravaglia et al., 2008), and that administration of a steroid may help to mitigate involvement of the immune system. In addition, we found that bortezomib-induced PN was most likely to manifest in male patients. To our knowledge, no reports of sex differences in CIPN have been described. Although Mileshkin et al. studied the occurrence of PN in patients treated with thalidomide, they also found no sex differences (Mileshkin et al., 2006). In terms of cancer pain, however, an earlier study reported that pain was significantly exacerbated when the patient was male (Kanbayashi et al., 2009). This issue of sex-related bortezomib-induced PN warrants further investigation.

Corso et al. concluded that the incidence, severity and outcome of bortezomib-induced PN are similar in untreated and pre-treated multiple myeloma (MM) patients (Corso et al., 2010). The only exception to this finding was a lower incidence and shorter duration of neuropathic pain in untreated patients with less frequent need for bortezomib discontinuation. The authors reported age to be the most relevant risk factor for bortezomib-induced PN, with a 6% PN risk increase for every additional year of age. Dimopoulos et al. demonstrated that bortezomib induced PN is dose-related and cumulative up to a ceiling and is consistently reversible in the majority of patients (Dimopoulos et al., 2011). In multivariate analysis, the authors found prior PN to be the only significant risk factor for bortezomib-induced PN in a newly diagnosed patient population. Importantly, there was no correlation in this study between occurrence of PN and reduced response rate or median time to progression (TTP). Lanzani et al. also indicated that the course of bortezomib-induced peripheral neurotoxicity can be severe in subjects with normal neurological examination at baseline, thereby suggesting careful monitoring during treatment in such patients (Lanzani et al., 2008). Their results confirm that pre-existing neuropathy is a risk factor for the development of more severe bortezomib-induced peripheral neurotoxicity and that severe PN may occur only after a few cycles of treatment. However, from the perspective of daily clinical practice, it is important to note that individual cases of severe bortezomib toxicity (in one case leading to drug treatment withdrawal only after two cycles of treatment) can also occur in naïve first-line patients or in pretreated patients with a normal neurological examination prior to bortezomib administration.

Furthermore, other studies have clarified the relationship between genetic factors and bortezomib-induced PN. Broyl et al. suggested an interaction between myeloma-related factors and the patient's genetic background in the development of CIPN, with different molecular pathways being implicated in bortezomib- and vincristine-induced PN (Broyl et al., 2010). Additionally, Favis et al. reported that genes associated with immune function (CTLA4, CTSS), reflexive coupling within Schwann cells (GJE1), drug binding (PSMB1), and neuron function (TCF4, DYNC1I1) were associated with bortezomib-induced PN (Favis et al., 2011).

### 2.2 Taxanes (paclitaxel, docetaxel)

The taxanes are intravenously administered microtubule stabilizing agents (MTSA) that interfere with mitotic spindles during cell mitosis. They include paclitaxel, docetaxel, and a new albumin-bound formulation of paclitaxel. This class is widely used in some of the most prevalent solid tumors including lung, breast, and prostate cancer, often in combination with platinum agents or after platinum treatment. Combination of a taxane and platinum is often first-line cancer treatment, and taxane monotherapy is reserved for refractory or metastatic disease settings. CIPN is more common with paclitaxel than docetaxel (Kannarkat G et al., 2007). Paclitaxel is a compound extracted from the Pacific yew tree Taxus brevifolia with antineoplastic activity. Paclitaxel binds to tubulin and inhibits the disassembly of microtubules, thereby resulting in the inhibition of cell division. This agent also induces apoptosis by binding to and blocking the function of the apoptosis inhibitor protein Bcl-2 (B-cell Leukemia 2) (National Cancer Institute., 2011). Docetaxel is a semi-synthetic, second-generation taxane derived from a compound found in the European yew tree Taxus baccata. Docetaxel displays potent and broad antineoplastic properties; it binds to and stabilizes tubulin, thereby inhibiting microtubule disassembly which results in cell-cycle arrest at the G2/M phase and cell death. This agent also inhibits pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and displays immunomodulatory and pro-inflammatory properties by inducing various mediators of the inflammatory response. Docetaxel has been studied for use as a radiation-sensitizing agent (National Cancer Institute., 2011).

The risk of PN due to administration of taxanes increased in concert with the number of cycles of chemotherapy (Kanbayashi et al., 2010). This result agrees with earlier studies which reported PN to be a dose-limiting factor in taxane therapy (Argyriou et al., 2008; Hagiwara & Sunada, 2004; Makino, 2004).

In a recent review paper discussing neuropathy induced by MTSA, neuropathies induced by taxanes were found to be the most extensively studied (Lee & Swain, 2006). This type of neuropathy usually presents as sensory neuropathy (SN) and is more common with paclitaxel than with docetaxel administration. The incidence of MTSA-induced neuropathy seems to depend on the MTSA dose per treatment cycle, the schedule of treatment, and the duration of the infusion. Although there have been several small clinical trials testing neuroprotective agents, early recognition and supportive care remain the best approaches for prevention and management of MTSA-induced neuropathy (Lee & Swain, 2006). In another review, Argyriou et al. found that the incidence of taxane-induced PN is related to possible causal factors, such as, a single dose per course and cumulative dose (Argyriou et al., 2008b; Fountzilas et al., 2004; Nabholtz et al., 1996; Smith et al., 1999**).** Specifically, Hilkens et al. reported that severe docetaxel neuropathy is most likely to occur following treatment with a cumulative dosage over 600 mg/m$^2$ (Hilkens et al., 1997). The risk of taxane-induced PN was also found to be related to treatment schedule, prior or concomitant administration of platinum compounds or vinca alcaloids, age and pre-existing PN due to heredity or medical conditions, such as DM, alcohol abuse, paraneoplastic syndromes, and others (Argyriou et al.,2008b; Chaudhry et al., 2003).

Although it has been previously proposed that elderly patients are more prone to higher risk of manifesting taxanes-induced PN (Akerley et al., 2003), our study did not find advanced age to be a predictor for taxane-induced PN. Argyriou et al. also indicated that elderly cancer patients did not have a greater risk of CIPN, nor was advanced age associated with worst severity of CIPN (Argyriou et al., 2006; Argyriou et al., 2008b).

In terms of infusion time, Markman reported that a 3-h infusion of paclitaxel is associated with a lower risk of neutropenia and a greater risk of PN, compared to either 24-h infusion paclitaxel or docetaxel (1-h infusion) (Markman, 2003). On the contrary, Mielke et al. observed a drastic increase in PN risk during the course of weekly paclitaxel administrations without significant differences between 1- and 3-h infusions (Mielke et al., 2003). This later finding is in contrast to pharmacokinetic observations indicating that a shortening of infusion time might enhance neurotoxicity by increasing the area under the curve of Cremophor (Mielke et al., 2003).

Some studies have also investigated the relationship between genetic factors and taxane-induced PN. In their pilot study, Sissung et al. suggested that paclitaxel-induced neuropathy and neutropenia might be linked to inherited variants of ABCB1 through a mechanism that is unrelated to altered plasma pharmacokinetics (Sissung et al., 2006). Specifically, polymorphisms that are associated with ABCB1 expression and function may be linked to treatment efficacy and the development of neutropenia and neurotoxicity in patients with androgen-independent prostate cancer receiving docetaxel. The authors also suggested that docetaxel-induced neuropathy, neutropenia grade, and overall survival could be linked to ABCB1 allelic variants with ensuing negative implications for docetaxel treatment in patients carrying ABCB1 variant genotypes (Sissung et al., 2008). Moreover, Mir et al. found a significant correlation between Glutathione-S-transferases P1 (GSTP1) (105) Ile/ (105) Ile genotype and the development of grade > or = 2 docetaxel -induced PN (Mir et al., 2009). Given that GSTs regulate the cellular response to oxidative stress, this finding strongly suggests a role for oxidative stress in the pathophysiology of docetaxel-induced PN.

### 2.3 Platinum-containing drugs (cisplatin, carboplatin, and oxaliplatin)

Platinum compounds covalently bind and damage DNA and include cisplatin, carboplatin, and oxaliplatin. These drugs are used in nearly all types of solid tumors. Though all three are known to cause classic symptoms of CIPN, higher incidences are seen with cisplatin and oxaliplatin. CIPN due to cisplatin is more often irreversible than in cases with oxaliplatin. CIPN is a dose-limiting toxicity with both cisplatin and oxaliplatin (Kannarkat G et al., 2007). Oxaliplatin will be primarily focused in this section.

Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1, 2-diaminocyclohexane (DACH) and with an oxalate ligand as a 'leaving group.' A 'leaving group' is an atom or a group of atoms that is displaced as a stable species taking with it the bonding electrons. After displacement of the labile oxalate ligand leaving group, active oxaliplatin derivatives, such as monoaquo and diaquo DACH platinum, alkylate macromolecules, forming both inter- and intra-strand platinum-DNA crosslinks, which result in inhibition of DNA replication and transcription and cell-cycle nonspecific cytotoxicity. The DACH side chain appears to inhibit alkylating-agent resistance (National Cancer Institute., 2011). Oxaliplatin is used for the treatment of colorectal, lung, breast and ovarian cancers. While oxaliplatin does not cause renal or hematologic toxicity, it can induce neuropathic pain which hampers the success of chemotherapy (Meyer et al., 2011). Oxaliplatin-induced PN (OXLIPN) is presented with two distinct syndromes, one of acute neurosensory toxicity and a chronic form that closely resembles the cisplatin-induced PN (Argyriou et al., 2008c). Oxaliplatin causes significant neurotoxicity that is experienced primarily in the hands during therapy and in the feet during follow-up. In a minority of patients the neurotoxicity is long lasting (Land et al., 2007).

The risk of OXLIPN increased as the number of drug administration cycles increased and when no non-steroidal anti-inflammatory drugs (NSAIDs) were co-administered (Kanbayashi et al., 2010). Thus, in agreement with prior reports, PN appears to be a dose-limiting factor in oxaliplatin therapy. As for an influence of NSAIDs, several groups have reported that cyclooxygenase (COX) 2-dependent prostaglandin (PG) E2 may be a causative factor in PN (Broom et al., 2004; Ma & Quirion, 2008; Suyama et al., 2004; Vo et al., 2009). Moreover, there have been reports that COX-2 is involved in diabetic PN, although that pathology is a separate entity to CIPN (Kellogg et al., 2007; Kellogg et al., 2008). Further investigation will be needed to elucidate the prophylactic efficacy of COX2-specific NSAIDs in relation to CIPN.

The incidence of OXLIPN is usually related to various risk factors, including treatment schedule, dosage, cumulative dose, infusion duration, and pre-existing peripheral neuropathy (Argyriou et al, 2008c). High cumulative doses of oxaliplatin are strongly associated with occurrence of chronic peripheral nerve damage, which could be attributed to the oxaliplatin dose accumulation. Indeed, it is documented that at cumulative doses that reach 800 mg/m$^2$, the occurrence of OXLIPN is highly likely; severe (grade 3) OXLIPN occurs in 15% after cumulative doses of 750–850 mg/m$^2$ and in 50% after a total dose of 1170 mg/m$^2$ (Grothey, 2005). Clinical and neurophysiological examinations of such cases show an acute and transient neurotoxicity and a cumulative dose-related sensory neuropathy in nearly all the patients (Pietrangeli et al., 2006). Pasetto et al. also reported that OXLIPN is usually late-onset and correlated with the cumulative-dose of oxaliplatin (Pasetto et al., 2006).

In another study, Brouwers et al. found that the severity of neuropathy secondary cisplatin administration was related to the cumulative dose and sodium thiosulfate use (Brouwers et al., 2009). However, OXLIPN did not appear to be related to the dose within the studied dose range. No relationship was demonstrated between risk of PN and platinum levels, renal function, glutathione transferase genotypes, DM, alcohol use, or co-medication. The authors concluded that since their study was explorative, the issues discussed need to be investigated further. In their retrospective analysis of 1587 cases, Ramanathan et al. indicated that oxaliplatin-based therapy does not influence the incidence, severity, or time to onset of peripheral sensory neuropathy in asymptomatic DM patients with colorectal cancer who meet eligibility criteria for clinical trials (Ramanathan et al., 2010). Attal et al. identified thermal hyperalgesia as a relevant clinical marker of early oxaliplatin neurotoxicity that may predict severe neuropathy (Attal et al., 2009).

Some studies have also investigated the connection between genetic polymorphisms and OXLIPN. Inada et al. suggested that ERCC1, C118T and GSTP1 Ile105Val polymorphisms are more strongly related to the time until onset of neuropathy than to the grade of neuropathy (Inada et al., 2010). This finding suggests that these polymorphisms influence patients' sensitivity to neuropathy. Antonacopoulou et al. reported that although ITGB3 L33P seems to be unrelated to the development of OXLIPN, it appears to be related to its severity (Antonacopoulou et al., 2010). Two independent studies in advanced colorectal cancer patients treated with oxaliplatin looked at the GST genes for patients who experienced grade 3 cumulative neuropathy (McWhinney et al., 2009; Ruzzo et al., 2007; Lecomte et al., 2006). Ruzzo et al. described an association between the GSTP1 105 Val G/G allele and the development of grade 3 neuropathy secondary to oxaliplatin treatment of 166 patients (Ruzzo et al., 2007). Additionally, Lecomte and colleagues reported a significant association between the GSTP1 105 Val G/G allele and risk of developing neurotoxicity in a

cohort of 64 patients (Lecomte et al., 2006). Gamelin et al. proposed that key components of the oxalate synthesis pathway could be associated with platinum-drug neurotoxicity (Gamelin et al., 2007). In their study of patients treated with oxaliplatin, a minor haplotype in glyoxylate aminotransferase (AGXT) predicted both acute and chronic neurotoxicity. Although this was the first study to indicate the contribution of AGXT, it warrants further analysis in larger patient cohorts. On the other hand, Argyriou et al. failed to provide evidence to support a causal relationship between the voltage-gated sodium channel gene SCN2A R19K polymorphism and OXLIPN (Argyriou et al., 2009).

### 2.4 Vinca alkaloids

Vinca alkaloids are plant-derived microtubule assembly inhibitors. This class includes vincristine, vinblastine and vinorelbine. Vincristine, the oldest and most neurotoxic of the class, is still widely used in leukemias, lymphomas, myeloma, and various sarcomas. CIPN is the most common dose-limiting toxicity of vincristine. Symptoms range from peripheral sensorimotor loss to autonomic dysfunction related to paralytic ileus, orthostasis, and sphincter problems. Central nervous system (CNS) involvement is much less common but can manifest as ataxia, cranial nerve palsies, cortical blindness and seizures. Vinblastine and vinorelbine have much lower incidences of neurotoxicity than their predecessor (Kannarkat G et al., 2007).

Vincristine is the sulfate salt of a natural alkaloid isolated from the plant Vinca rosea Linn with antimitotic and antineoplastic activities. Vincristine binds irreversibly to microtubules and spindle proteins in S phase of the cell cycle and interferes with the formation of the mitotic spindle, thereby arresting tumor cells in metaphase. This agent also depolymerizes microtubules and may also interfere with amino acid, cyclic AMP, and glutathione metabolism; calmodulin-dependent Ca++ -transport ATPase activity; cellular respiration; and nucleic acid and lipid biosynthesis (National Cancer Institute., 2011).

The risk of CIPN due to vincristine administration increased as the number of chemotherapy cycles increased (Kanbayashi et al., 2010). This result supports earlier reports that concluded vincristine-induced PN (VIPN) to be a dose-limiting factor of therapy (Ja'afer et al., 2006; Verstappen et al., 2005; Weintraub et al., 1996). Moreover, analgesic adjuvants used to relieve the symptoms of PN during chemotherapy did not show adequate prophylactic efficacy. Thus, in agreement with prior studies (Kannarkat et al., 2007; Ocean et al., 2004; Park et al.,2008; Walker et al., 2007; Windebank et al., 2008; Wolf et al., 2008) it can be concluded that no effective analgesic adjuvants are currently available for CIPN. Verstappen et al. reported that while neuropathic changes were observed in both dose intensity groups, the higher dose intensity group reported significantly more symptoms during therapy, whereas neurologic signs were significantly more prominent after a cumulative dose of 12 mg vincristine (Verstappen et al., 2005). Furthermore, off-therapy exacerbation of symptoms (24%) and signs (30%) occurred unexpectedly in that trial. Weintraub et al. reported that colony-stimulating factors could precipitate a severe atypical neuropathy when given in conjunction with vincristine (Weintraub et al, 1996). The development of this severe atypical neuropathy was most strongly associated with the cumulative dose of vincristine. Conversely, the size of individual doses and the number of doses given in cycle 1 were important only to the extent that they influenced the cumulative dose.

Studies have also attempted to clarify the relationship between genetic factors and VIPN. For example, Egbelakin et al. evaluated the relationship between cytochrome P450 (CYP)

3A5 genotype and VIPN in children with precursor B cell acute lymphoblastic leukemia (preB ALL) (Egbelakin et al., 2011). They concluded that CYP3A5 expressers experience less VIPN, produce more primary metabolite (M1), and have lower metabolic ratios compared to CYP3A5 non-expressers. Broyl et al. reported that early-onset VIPN was characterized by the up-regulation of genes involved in cell cycle and proliferation, including AURKA and MKI67, and also by the presence of single-nucleotide polymorphisms (SNPs) in genes involved in these processes, such as GLI1 (rs2228224 and rs2242578) (Broyl et al., 2010). In this study, late-onset VIPN was associated with the presence of SNPs in genes involved in absorption, distribution, metabolism, and excretion. Graf et al. showed that a 17p11.2-12 duplication predisposed patients to severe neurotoxicity from vincristine, suggesting that this drug should be avoided in patients with CMT1A (Graf et al., 1996). Thus, it is essential to obtain a detailed family history for all oncology patients to screen for possible hereditary neuropathies. In patients with unexplained or preexisting familial neuropathy, testing for 17p11.2-12 duplication should be carried out prior to initiating vincristine therapy. Patients with other hereditary neuropathies may also be at risk for severe neurotoxic reactions.

### 2.5 Thalidomide

Thalidomide is a synthetic derivative of glutamic acid (alpha-phthalimido-glutarimide) with teratogenic, immunomodulatory, anti-inflammatory and anti-angiogenic properties. Thalidomide acts primarily by inhibiting both the production of tumor necrosis factor alpha (TNF-alpha) in stimulated peripheral monocytes and the activities of interleukins and interferons. This agent also inhibits polymorphonuclear chemotaxis and monocyte phagocytosis. In addition, thalidomide inhibits pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), thereby inhibiting angiogenesis (National Cancer Institute., 2011).

Harland et al. concluded that changes in nerve conductivity were a frequent but unpredictable adverse effect of thalidomide (< or = 200 mg/day), and that smoking might protect against such changes (Harland et al., 1995). The authors suggested that nerve conduction studies are required before and during treatment, irrespective of the prescribed dose. Molloy et al. found that thalidomide neuropathy occurred concurrently with a decline in the sensory nerve action potential (SNAP) index (Molloy et al., 2001). Thus, the SNAP index can be used to monitor PN, but not for early detection. Older age and cumulative dose were possible contributing factors for thalidomide-induced PN. Neuropathy may thus be a common complication of thalidomide therapy in older patients. Bastuji-Garin et al. found the risk of thalidomide neuropathy seems to be negligible for doses less than 25 mg per day, regardless of the duration of therapy (Bastuji-Garin et al., 2002). In patients with advanced MM, a thalidomide daily dose of 150 mg was found to minimize PN without jeopardizing response and survival (Offidani et al., 2004). Torsi et al. reported that the severity of neurotoxicity was not related to cumulative or daily thalidomide dose, but only to the duration of the disease prior to thalidomide treatment (Torsi et al., 2005). However, no patients presented with neurological symptoms at study entry. The results of this study suggest that long-term thalidomide therapy in MM may be hampered by the remarkable neurotoxicity of the drug, and that a neurological evaluation should be mandatory prior to thalidomide treatment, in order to identify patients at risk of developing a PN. Others suggest that the majority of patients would develop PN given sufficient length of treatment with thalidomide (Mileshkin et al., 2006). Accordingly, therapy should be limited to less

than 6 months in order to minimize the risk of neurotoxicity. These authors also found that electrophysiologic monitoring provides no clear benefit versus careful clinical evaluation for the development of clinically significant neuropathy. On the other hand, Souayah et al. reported that symptom severity was correlated with the time of onset, but not with cumulative dose (Souayah et al., 2010). In this study, five patients partially improved when the thalidomide was withdrawn, and three patients developed tremor with the neuropathy. Since the sensory symptoms occurred shortly after thalidomide was introduced, it is advisable that older patients with macular degeneration be carefully screened for risk factors of PN before thalidomide is used in their treatment.

Finally, a number of studies investigated the relationship between genetic factors and thalidomide-induced PN. Johnson et al. demonstrated that an individual's risk of developing a PN after thalidomide treatment could be mediated by polymorphisms in genes governing repair mechanisms and inflammation in the peripheral nervous system (Johnson et al., 2011). These authors concluded that their findings could contribute to the development of future neuroprotective strategies with thalidomide therapy. Finally, Cibeira et al. found that a polymorphism in GSTT1 (rs4630) was associated with a lower frequency of thalidomide-induced PN (p=0.04) (Cibeira et al., 2011).

## 3. Conclusion

Although various analgesic adjuvants, including antidepressants and anti-epileptics, have been tested as therapeutic agents for CIPN, none have shown clear efficacy. Our results supported this notion, with CIPN occurring even with co-administration of analgesic adjuvants. Despite previous reports showing an opioid to effectively relieve PN (Gatti et al., 2009; Watson et al., 2003), the lack of co-administration of opioids was not identified as a predictor for CIPN (Kanbayashi et al., 2010). Further research is warranted in regard to the potential prophylactic effects of agents such as steroids, NSAIDs (particularly COX2-specific NSAIDs), gabapentinoids (gabapentin or pregabalin) and opioids on the development of CIPN (Attal et al., 2006; Rao et al., 2007; Tsavaris et al., 2008; Vanotti et al., 2007; Vondracek et al.,2009). Risk factors for CIPN such as gene polymorphism have already been reported, but the interrelationship of CIPN and gene polymorphism in particular will need to be verified at a later date. Further investigation of these issues will be needed to establish evidence-based medicine in the prophylaxis of CIPN and improve QOL for patients undergoing chemotherapy.

## 4. References

Akerley, W., Herndon, JE., Egorin, MJ., Lyss, AP., Kindler, HL., Savarese, DM., Sherman, CA., Rosen, DM., Hollis, D., Ratain, MJ., & Green, MR. (2003). Weekly, high-dose paclitaxel in advanced lung carcinoma: a phase II study with pharmacokinetics by the Cancer and Leukemia Group B. *Cancer,* Vol.97, No.10, (May 2003), pp. (2480-6), ISSN 0008-543X

Antonacopoulou, AG., Argyriou AA., Scopa CD., Kottorou A., Kominea A., Peroukides, S., & Kalofonos, HP. (2010). Integrin beta-3 L33P: a new insight into the pathogenesis of chronic oxaliplatin-induced peripheral neuropathy? *Eur J Neurol,* Vol.17, No.7, (July 2010), pp. (963-8), ISSN 1351-5101

Attal, N., Cruccu, G., Haanpää, M., Hansson, P., Jensen, TS., Nurmikko, T., Sampaio, C., Sindrup, S., & Wiffen, P., EFNS Task Force. (2006). EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol*, Vol.13, No.11, (November 2006), pp. (1153-69), ISSN 1351-5101

Argyriou, AA., Polychronopoulos, P., Koutras, A., Iconomou, G., Gourzis, P., Assimakopoulos, K., Kalofonos, HP., & Chroni, E. (2006). Is advanced age associated with increased incidence and severity of chemotherapy-induced peripheral neuropathy? *Support Care Cancer*, Vol.14, No.3, (March 2006), pp. (223-9), ISSN 0941-4355

Argyriou, AA., Iconomou, G., & Kalofonos, HP. (2008a) Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. *Blood,* Vol.112, No.5, (September 2008), pp. (1593-9), ISSN 0006-4971

Argyriou, AA., Koltzenburg, M., Polychronopoulos, P., Papapetropoulos, S., & Kalofonos, HP. (2008b). Peripheral nerve damage associated with administration of taxanes in patients with cancer. *Crit Rev Oncol Hematol,* Vol.66, No.3, (June 2008), pp. (218-28), ISSN 1040-8428

Argyriou, AA., Polychronopoulos, P., Iconomou, G., Chroni, E. & Kalofonos, HP. (2008c). A review on oxaliplatin-induced peripheral nerve damage. *Cancer Treat Rev*, Vol.34, No.4, (June 2008), pp. 368-77, ISSN 0305-7372

Argyriou, AA., Antonacopoulou, AG., Scopa, CD., Kottorou, A., Kominea, A., Peroukides, S., & Kalofonos, HP. (2009). Liability of the voltage-gated sodium channel gene SCN2A R19K polymorphism to oxaliplatin-induced peripheral neuropathy. *Oncology,* Vol.77, No.3-4, pp. (254-6), ISSN 0030-2414

Attal, N., Bouhassira, D., Gautron, M., Vaillant, JN., Mitry, E., Lepère, C., Rougier, P., & Guirimand, F. (2009). Thermal hyperalgesia as a marker of oxaliplatin neurotoxicity: a prospective quantified sensory assessment study. *Pain*, Vol.144, No.3, (August 2009), pp. (245-52), ISSN 0304-3959

Badros, A., Goloubeva, O., Dalal, JS., Can, I., Thompson, J., Rapoport, AP., Heyman, M., Akpek, G., & Fenton, RG. (2007). Neurotoxicity of bortezomib therapy in multiple myeloma: a single-center experience and review of the literature. *Cancer,* Vol.110, No.5, (September 2007), pp. (1042-9) ISSN 0008-543X

Broom, DC., Samad, TA., Kohno, T., Tegeder, I., Geisslinger, G., & Woolf, CJ. (2004). Cyclooxygenase 2 expression in the spared nerve injury model of neuropathic pain. *Neuroscience*, Vol.124, No.4, (June 2004), pp. (891-900), ISSN 0306-4522

Bastuji-Garin, S., Ochonisky, S., Bouche, P., Gherardi, RK., Duguet, C., Djerradine, Z., Poli, F., & Revuz, J., Thalidomide Neuropathy Study Group.(2002). Incidence and risk factors for thalidomide neuropathy: a prospective study of 135 dermatologic patients. *J Invest Dermatol,* Vol.119, No.5, (November 2002), pp. (1020-6), ISSN 0022-202X

Brouwers, EE., Huitema, AD., Boogerd, W., Beijnen, JH., & Schellens, JH. (2009). Persistent neuropathy after treatment with cisplatin and oxaliplatin. *Acta Oncol*, Vol.48, No.6, pp. (832-41), ISSN 0284-186X

Broyl, A., Corthals, SL., Jongen, JL., van der Holt, B., Kuiper, R., de Knegt, Y., van Duin, M., el Jarari, L., Bertsch, U., Lokhorst, HM., Durie, BG., Goldschmidt, H., & Sonneveld, P. (2010). Mechanisms of peripheral neuropathy associated with bortezomib and vincristine in patients with newly diagnosed multiple myeloma: a prospective analysis of data from the HOVON-65/GMMG-HD4 trial. *Lancet Oncol,* Vol.11, No.11, (November 2010), pp. (1057-65) ISSN 1470-2045

Chaudhry, V., Chaudhry, M., Crawford, TO., Simmons-O'Brien, E., & Griffin, JW. (2003). Toxic neuropathy in patients with pre-existing neuropathy. *Neurology*, Vol.60, No.2, (January 2003), pp. (337-40), ISSN 0028-3878

Cibeira, MT., Fernández de Larrea, C., Navarro, A., Díaz, T., Fuster, D., Tovar, N., Rosiñol, L., Monzó, M., & Bladé, J. (2011). Impact on response and survival of DNA repair single nucleotide polymorphisms in relapsed or refractory multiple myeloma patients treated with thalidomide. *Leuk Res*, ISSN 0145-2126

Corso, A., Mangiacavalli, S., Varettoni, M.; Pascutto, C.; Zappasodi, P., & Lazzarino, M. (2010). Bortezomib-induced peripheral neuropathy in multiple myeloma: a comparison between previously treated and untreated patients. *Leuk Res*, Vol.34, No.4, (April 2010), pp. (471-4), ISSN 0145-2126

Dimopoulos, MA., Mateos, MV., Richardson, PG., Schlag, R., Khuageva, NK., Shpilberg, O., Kropff ,M., Spicka, I., Palumbo, A., Wu, KL., Esseltine, DL., Liu, K., Deraedt, W., Cakana, A., Van De Velde, H., & San Miguel, JF. (2011). Risk factors for, and reversibility of,peripheral neuropathy associated with bortezomib-melphalan-prednisone in newly diagnosed patients with multiple myeloma: subanalysis of the phase 3 VISTA study. *Eur J Haematol,* Vol.86, No.1, (January 2011), pp. (23-31), ISSN 0902-4441

Egbelakin, A., Ferguson, MJ., MacGill, EA., Lehmann, AS., Topletz, AR., Quinney, SK., Li, L., McCammack, KC., Hall, SD., & Renbarger, JL.(2011). Increased risk of vincristine neurotoxicity associated with low CYP3A5 expression genotype in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer,* Vol.56, No.3, (March 2011), pp. (361-7), ISSN 1545-5009

Favis, R., Sun, Y., van de Velde, H., Broderick, E., Levey, L., Meyers, M., Mulligan, G., Harousseau, JL., Richardson, PG., & Ricci, DS. (2011). Genetic variation associated with bortezomib-induced peripheral neuropathy. *Pharmacogenet Genomics*, Vol.21, No.3, (March 2011), pp. (121-9), ISSN 1744-6872

Fountzilas, G., Kalofonos, HP., Dafni, U., Papadimitriou, C., Bafaloukos, D., Papakostas, P., Kalogera-Fountzila, A., Gogas, H., Aravantinos, G., Moulopoulos, LA., Economopoulos, T., Pectasides, D., Maniadakis, N.; Siafaka, V.; Briasoulis, E.; Christodoulou, C.; Tsavdaridis, D.; Makrantonakis, P.; Razis, E.; Kosmidis, P.; Skarlos, D., & Dimopoulos, MA. (2004). Paclitaxel and epirubicin versus paclitaxel and carboplatin as first-line chemotherapy in patients with advanced breast cancer: a phase III study conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol,* Vol.15, No.10, (October 2004), pp. (1517–26), ISSN 0923-7534

Gatti, A.; Sabato, AF.; Occhioni, R.; Colini Baldeschi, G., & Reale, C. (2009). Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicenter Italian study. *Eur Neurol,* Vol.61, No.3, pp. (129-37), ISSN 0014-3022

Gamelin L., Capitain, O., Morel, A., Dumont, A., Traore, S., Anne le, B., Gilles, S., Boisdron-Celle, M., & Gamelin, E. (2007). Predictive factors of oxaliplatin neurotoxicity: the involvement of the oxalate outcome pathway. *Clin Cancer Res*, Vol.13, No.21, (November 2007), pp. (6359-68), ISSN 1078-0432

Graf, WD., Chance, PF., Lensch, MW., Eng, LJ., Lipe, HP., & Bird, TD. (1996). Severe vincristine neuropathy in Charcot-Marie-Tooth disease type 1A. *Cancer,* Vol.77, No.7, (April 1996), pp. (1356-62), ISSN 0008-543X

Grothey, A. (2005). Clinical management of oxaliplatin-associated neurotoxicity. *Clin Colorectal Cancer,* Vol.5, Suppl 1, (April 2005), pp. (S38-46), ISSN 1533-0028

Hagiwara, H., & Sunada, Y. (2004). Mechanism of taxane neurotoxicity. *Breast Cancer,* Vol.11, No.1, pp. (82-5), ISSN 1340-6868

Harland, CC., Steventon, GB., & Marsden, JR. (1995). Thalidomide-induced neuropathy and genetic differences in drug metabolism. *Eur J Clin Pharmacol,* Vol.49, No.1-2, pp. (1-6), ISSN0031-6970Hilkens, PH., Verweij, J., Vecht, CJ., Stoter, G., & van den Bent, MJ. (1997). Clinical characteristics of severe peripheral neuropathy induced by docetaxel (Taxotere). *Ann Oncol,* Vol.8, No.2, (February 1997), pp. (187-90), ISSN 0923-7534

Inada, M., Sato, M., Morita, S., Kitagawa, K., Kawada, K., Mitsuma, A., Sawaki, M., Fujita, K., & Ando, Y. (2010). Associations between oxaliplatin-induced peripheral neuropathy and polymorphisms of the ERCC1 and GSTP1 genes. *Int J Clin Pharmacol Ther,* Vol.48, No.11, (November 2010), pp. (729-34), ISSN 0946-1965

Ja'afer, FM., Hamdan, FB., & Mohammed, FH. (2006).Vincristine-induced neuropathy in rat: electrophysiological and histological study. *Exp Brain Res,* Vol.173, No.2, (August 2006), pp. (334-45), ISSN 0014-4819Johnson, DC., Corthals, SL., Walker, BA., Ross, FM., Gregory, WM., Dickens, NJ., Lokhorst, HM., Goldschmidt, H., Davies, FE., Durie, BG., Van Ness, B., Child, JA., Sonneveld, P., & Morgan, GJ. (2011). Genetic factors underlying the risk of thalidomide-related neuropathy in patients with multiple myeloma. *J Clin Oncol,* Vol.29, No.7, (March 2011), pp. (797-804), ISSN 0732-183X

Kanbayashi, Y., Okamoto, K., Ogaru, T., Hosokawa, T., & Takagi, T. (2009). Statistical validation of the relationships of cancer pain relief with various factors using ordered logistic regression analysis. *Clin J Pain,* Vol.25, No.1, (January 2009), pp. (65-72), ISSN 0749-8047

Kanbayashi, Y., Hosokawa, T., Okamoto, K., Konishi, H., Otsuji, E., Yoshikawa, T., Takagi, T., & Taniwaki ,M. (2010). Statistical identification of predictors for peripheral neuropathy associated with administration of bortezomib, taxanes, oxaliplatin or vincristine using ordered logistic regression analysis. *Anticancer Drugs,* Vol.21, No.9, (October 2010), pp. (877-81), ISSN 0959-4973

Kannarkat, G., Lasher, EE., & Schiff, D. (2007). Neurologic complications of chemotherapy agents. *Curr Opin Neurol,*Vol.20,No.6, (December 2007), pp. (719-25), ISSN 1350-7540

Kellogg, AP., Cheng, HT., & Pop-Busui, R. (2008). Cyclooxygenase-2 pathway as a potential therapeutic target in diabetic peripheral neuropathy. *Curr Drug Targets,* Vol.9, No.1, (January 2008), pp. (68-76), ISSN 1389-4501

Kellogg, AP., Wiggin, TD., Larkin, DD., Hayes, JM., Stevens MJ., & Pop-Busui R. (2007). Protective effects of cyclooxygenase-2 gene inactivation against peripheral nerve dysfunction and intraepidermal nerve fiber loss in experimental diabetes. *Diabetes,* Vol.56, No.12, (December 2007), pp. (2997-3005), ISSN 0012-1797

Land, SR., Kopec, JA., Cecchini, RS., Ganz, PA., Wieand, HS., Colangelo, LH., Murphy, K., Kuebler, JP., Seay, TE., Needles, BM., Bearden, JD 3rd., Colman, LK., Lanier, KS., Pajon, ER Jr., Cella, D., Smith, RE., O'Connell, MJ.; Costantino, JP., & Wolmark, N. (2007). Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07. *J Clin Oncol,* Vol.25, No.16, (June 2007), pp. (2205-11), ISSN 0732-183X

Lanzani, F., Mattavelli, L., Frigeni, B., Rossini, F., Cammarota, S., Petrò, D., Jann, S., & Cavaletti, G. (2008). Role of a pre-existing neuropathy on the course of bortezomib-induced peripheral neurotoxicity. *J Peripher Nerv Syst,* Vol.13, No.4, (December 2008), pp. (267-74), ISSN 1085-9489

Lecomte, T., Landi, B., Beaune, P., Laurent-Puig, P., & Loriot, MA. (2006). GlutathioneS-transferase P1 polymorphism (Ile105Val) predicts cumulative neuropathy in patients receiving oxaliplatin-based chemotherapy. *Clin Cancer Res* ,Vol.12,No.10, (May 2006), pp. (3050-6), ISSN 1078-0432Lee, JJ. & Swain, SM. (2006). Peripheral neuropathy induced by microtubule-stabilizing agents. *J Clin Oncol,* Vol.24, No.10, (April 2006), pp. 1633-42, ISSN 0732-183X

Ma, W., & Quirion, R. (2008). Does COX2-dependent PGE2 play a role in neuropathic pain? *Neurosci Lett,* Vol.437, No.3, (June 2008), pp. (165-9), ISSN 0304-3940

Makino, H. (2004). Treatment and care of neurotoxicity from taxane anticancer agents. *Breast Cancer,* Vol.11, No.1, pp. (100-4), ISSN 1340-6868

Markman, M. (2003). Management of toxicities associated with the administration of taxanes. *Expert Opin Drug Saf,* Vol.2, No.2, (March 2003), pp. (141-6), ISSN 1474-0338

McWhinney, SR., Goldberg, RM., & McLeod, HL. (2009).Platinum neurotoxicity pharmacogenetics. Platinum neurotoxicity pharmacogenetics. *Mol Cancer Ther,* Vol.8, No.1, (January 2009), pp. (10-6), ISSN 1535-7163

Meyer, L., Patte-Mensah, C., Taleb, O., & Mensah-Nyagan, AG. (2011). Allopregnanolone prevents and suppresses oxaliplatin-evoked painful neuropathy: multi-parametric assessment and direct evidence. *Pain* ,Vol.152, No.1, (January 2011), pp. (170-81), ISSN 0304-3959

Mielke, S., Mross, K., Gerds, TA., Schmidt, A., Wäsch, R., Berger, DP., Lange, W., & Behringer, D. (2003). Comparative neurotoxicity of weekly non-break paclitaxel infusions over 1 versus 3 h. *Anticancer Drugs,* Vol.14, No.10, (November 2003), pp. (785-92), ISSN 0959-4973

Mileshkin, L., Stark, R., Day, B., Seymour, JF., Zeldis, JB., & Prince, HM. (2006). Development of neuropathy in patients with myeloma treated with thalidomide: patterns of occurrence and the role of electrophysiologic monitoring. *J Clin Oncol,* Vol.24, No.27, (September 2006), pp. (4507-14), ISSN 0732-183X

Mir, O., Alexandre, J., Tran, A., Durand, JP., Pons, G., Treluyer, JM., & Goldwasser, F. (2009). Relationship between GSTP1 Ile (105) Val polymorphism and docetaxel-induced peripheral neuropathy: clinical evidence of a role of oxidative stress in taxane toxicity. *Ann Oncol,* Vol.20, No.4, (April 2009), pp. (736-40), ISSN 0923-7534

Molloy, FM., Floeter, MK., Syed, NA., Sandbrink, F., Culcea, E., Steinberg, SM., Dahut, W., Pluda, J., Kruger, EA., Reed, E., & Figg, WD. (2001). Thalidomide neuropathy in patients treated for metastatic prostate cancer. *Muscle Nerve,* Vol.24, No.8, (August 2001), pp. (1050-7), ISSN 0148-639X

Nabholtz, JM., Gelmon, K., Bontenbal, M.; Spielmann, M.; Catimel, G.; Conte, P.; Klaassen, U.; Namer, M.; Bonneterre, J.; Fumoleau, P., & Winograd, B. (1996). Multicenter randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. *J Clin Oncol*, Vol.14, No.6, (June 1996), pp. (1858–67), ISSN 0732-183X

National Cancer Institute (2011). National Cancer Institute of the National Institutes of Health (NIH).Cancer topics, In: *Cancer Drug Information,* accessed 25 June 2011, Available from: *http://www.cancer.gov/cancertopics/druginfo/alphalist*

Ocean, AJ., & Vahdat, LT. (2004). Chemotherapy-induced peripheral neuropathy: pathogenesis and emerging therapies. *Support Care Cancer,* Vol.12, No.9, (September 2004), pp. (619-25), ISSN 0941-4355

Offidani, M., Corvatta, L., Marconi, M., Malerba, L., Mele, A., Olivieri, A., Brunori, M., Catarini, M., Candela, M., Capelli, D., Montanari, M., Rupoli, S., & Leoni, P. (2004). Common and rare side-effects of low-dose thalidomide in multiple myeloma: focus on the dose-minimizing peripheral neuropathy. *Eur J Haematol,* Vol.72, No.6, (June 2004), pp. (403-9), ISSN 0902-4441

Park, SB., Krishnan, AV., Lin, CS., Goldstein, D., Friedlander, M., & Kiernan, MC. (2008). Mechanisms underlying chemotherapy-induced neurotoxicity and the potential for neuroprotective strategies. *Curr Med Chem,* Vol.15, No.29, pp. (3081-94), ISSN 1568-0142

Pasetto, LM., D'Andrea, MR., Rossi, E., & Monfardini, S. (2006). Oxaliplatin-related neurotoxicity: how and why? *Crit Rev Oncol Hematol,* Vol.59, No.2, (August 2006), pp. (159-68), ISSN 1040-8428

Pei, XY., Dai ,Y., Grant, S.(2004). Synergistic induction of oxidative injury and apoptosis in human multiple myeloma cells by the proteasome inhibitor bortezomib and histone deacetylase inhibitors. *Clin Cancer Res,* Vol.10, No.11, (June 2004), pp. (3839-52), ISSN 1078-0432

Pietrangeli, A., Leandri, M., Terzoli, E., Jandolo, B., & Garufi, C. (2006). Persistence of high-dose oxaliplatin-induced neuropathy at long-term follow-up. *Eur Neurol,* Vol.56, No.1, pp. (13-6), ISSN 0014-3022

Ramanathan, RK., Rothenberg, ML., de Gramont, A., Tournigand, C., Goldberg, RM., Gupta, S., & André, T. (2010). Incidence and evolution of oxaliplatin-induced peripheral sensory neuropathy in diabetic patients with colorectal cancer: a pooled analysis of three phase III studies. *Ann Oncol*, Vol.21, No.4, (April 2010), pp. (754-8), ISSN 0923-7534

Rao, RD., Michalak, JC., Sloan, JA., Loprinzi, CL., Soori, GS., Nikcevich, DA., Warner, DO., Novotny, P., Kutteh, LA., & Wong, GY., North Central Cancer Treatment Group. (2007). Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled crossover trial (N00C3). *Cancer*, Vol.110, No.9, (November 2007), pp. (2110-8), ISSN 0008-543X

Ravaglia, S., Corso, A., Piccolo, G., Lozza, A.; Alfonsi, E.; Mangiacavalli, S., Varettoni, M., Zappasodi, P., Moglia, A., Lazzarino, M., & Costa, A. (2008). Immune-mediated neuropathies in myeloma patients treated with bortezomib. *Clin Neurophysiol,* Vol.119, No.11, (November 2008), pp. (2507-12), ISSN 1388-2457

Ruzzo, A., Graziano, F., Loupakis, F., Rulli, E., Canestrari, E., Santini, D., Catalano, V., Ficarelli, R., Maltese, P., Bisonni, R., Masi, G., Schiavon, G., Giordani, P., Giustini, L., Falcone, A., Tonini, G., Silva, R., Mattioli, R., Floriani, I., & Magnani, M. (2007). Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. *J Clin Oncol,* Vol.25, No.10, (April 2007), pp. (1247-54), ISSN 0732-183X

Sissung, TM., Mross, K., Steinberg, SM., Behringer, D., Figg, WD., Sparreboom, A., & Mielke, S. (2006). Association of ABCB1 genotypes with paclitaxel-mediated peripheral neuropathy and neutropenia. *Eur J Cancer,* Vol.42, No.17, (November 2006), pp. (2893-6), ISSN 0959-8049

Sissung, TM., Baum, CE., Deeken, J., Price, DK., Aragon-Ching, J., Steinberg, SM., Dahut, W., Sparreboom, A., & Figg, WD. (2008). ABCB1 genetic variation influences the toxicity and clinical outcome of patients with androgen-independent prostate cancer treated with docetaxel. *Clin Cancer Res,* Vol.14, No.14, (July 2008), pp. (4543-9) ISSN 1078-0432

Smith, RE., Brown, AM., Mamounas, EP., Anderson, SJ., Lembersky, BC., Atkins, JH., Shibata, HR., Baez, L., DeFusco, PA., Davila, E., Tipping, SJ., Bearden, JD., & Thirlwell, MP. (1999). Randomized trial of 3-hour versus 24-hour infusion of high-dose paclitaxel in patients with metastatic or locally advanced breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-26. *J Clin Oncol,* Vol.17, No.11, (November 1999), pp. (3403–11), ISSN 0732-183X

Souayah, N., & Khella, SL. (2010). A prospective double-blind, placebo-controlled study of thalidomide sensory symptoms in an elderly population with age-related macular degeneration. *J Clin Neurosci,* Vol.17, No.5, (May 2010), pp. (571-3), ISSN 0967-5868

Suyama, H., Kawamoto, M., Gaus, S., & Yuge, O. (2004). Effect of etodolac, a COX-2 inhibitor, on neuropathic pain in a rat model. *Brain Res,* Vol.1010, No.1-2, (June 2004), pp. (144-50), ISSN 0006-8993

Tosi, P., Zamagni, E., Cellini, C., Plasmati, R., Cangini, D., Tacchetti, P., Perrone, G., Pastorelli, F., Tura, S., Baccarani, M., & Cavo, M. (2005). Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. *Eur J Haematol*, Vol.74, No.3, (March 2005), pp. (212-6), ISSN 0902-4441

Tsavaris, N., Kopterides, P., Kosmas, C., Efthymiou, A., Skopelitis, H., Dimitrakopoulos, A., Pagouni, E., Pikazis, D., Zis, PV., & Koufos, C. (2008). Gabapentin monotherapy for the treatment of chemotherapy-induced neuropathic pain: a pilot study. *Pain Med*, Vol.9, No.8, (November 2008), pp. (1209-16), ISSN 1526-2375

Vanotti, A., Osio, M., Mailland, E., Nascimbene, C., Capiluppi, E., & Mariani, C. (2007). Overview on pathophysiology and newer approaches to treatment of peripheral neuropathies. *CNS Drugs*, Vol.21, Suppl 1, pp. (3-12), ISSN 1172-7047

Verstappen, CC., Koeppen, S., Heimans, JJ., Huijgens, PC., Scheulen, ME., Strumberg, D., Kiburg ,B., & Postma, TJ.(2005). Dose-related vincristine-induced peripheral neuropathy with unexpected off-therapy worsening. *Neurology*, Vol.64, No.6, (March 2005), pp. (1076-7), ISSN 0028-3878

Vo, T., Rice, AS., & Dworkin, RH. (2009). Non-steroidal anti-inflammatory drugs for neuropathic pain: how do we explain continued widespread use? *Pain,* Vol.143, No.3, (June 2009), pp. (169-71), ISSN 0304-3959

Vondracek, P., Oslejskova, H., Kepak, T., Mazanek, P., Sterba, J., Rysava, M., & Gal, P. (2009). Efficacy of pregabalin in neuropathic pain in paediatric oncological patients. *Eur J Paediatr Neurol,* Vol.13, No.4, (July 2009), pp. (332-6), ISSN 1090-3798

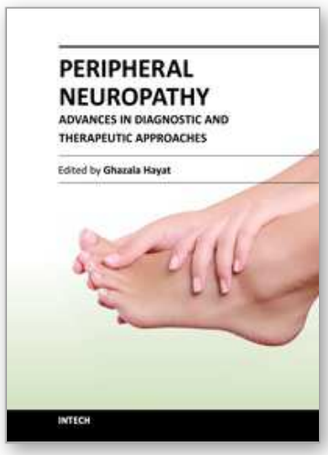
Walker, M., & Ni, O. (2007). Neuroprotection during chemotherapy: a systematic review. *Am J Clin Oncol ,* Vol.30,No.1, (February 2007), pp. (82-92), ISSN 0277-3732

Watson, CP., Moulin, D., Watt-Watson, J., Gordon, A., & Eisenhoffer J. (2003). Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain,* Vol.105, No.1-2, (September 2003), pp. (71-8), ISSN 0304-3959

Weintraub, M., Adde, MA., Venzon, DJ., Shad, AT., Horak, ID., Neely, JE., Seibel, NL., Gootenberg, J., Arndt, C., Nieder, ML., & Magrath, IT. (1996). Severe atypical neuropathy associated with administration of hematopoietic colony-stimulating factors and vincristine. *J Clin Oncol,* Vol.14, No.3, (March 1996), pp. (935-40), ISSN 0732-183X

Windebank, AJ., & Grisold, W. (2008). Chemotherapy-induced neuropathy. *J Peripher Nerv Syst,* Vol.13, No. 1, (March 2008), pp. (27-46), ISSN 1085-9489

Wolf, S., Barton, D., Kottschade L., Grothey A., & Loprinzi C. (2008). Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. *Eur J Cancer,* Vol.44, No.11, (July 2008), pp. (1507-15), ISSN 0961-5423




**Peripheral Neuropathy - Advances in Diagnostic and Therapeutic Approaches**

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Over the last two decades we have seen extensive progress within the practice of neurology. We have refined our understanding of the etiology and pathogenesis for both peripheral and central nervous system diseases, and developed new therapeutic approaches towards these diseases. Peripheral neuropathy is a common disorder seen by many specialists and can pose a diagnostic dilemma. Many etiologies, including drugs that are used to treat other diseases, can cause peripheral neuropathy. However, the most common cause is Diabetes Mellitus, a disease all physicians encounter. Disability due to peripheral neuropathy can be severe, as the patients suffer from symptoms daily. This book addresses the advances in the diagnosis and therapies of peripheral neuropathy over the last decade. The basics of different peripheral neuropathies is briefly discussed, however, the book focuses on topics that address new approaches to peripheral neuropathies.



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