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	χ^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.

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薬物療法

薬物療法の位置づけ

依存症に対して，さまざまな薬物療法が行われている．しかし，依存症の中心的症状である精神依存の治療において，薬物療法は主役ではない[1]．患者と治療者間の信頼関係の構築や，精神療法，集団精神療法，地域での支援などが基本であり，薬物療法は補助療法であってこれらの他の治療法と組み合わせることで有効性を発揮する．また，治療薬に依存する例も少なくないので，注意が必要である．さらに，問題薬物の種類，治療の段階，合併症など，患者の一人一人の状態に合わせて治療する必要がある．ただし，他の多くの精神疾患とは異なり，物質使用障害は，依存性物質が特定の標的分子に作用することによって引き起こされる障害なので，標的分子に作用する薬物などによって将来的には治療できるようになると期待される．

物質使用障害の治療ガイドラインが米国精神医学会から示されているが[2]，アルコール，コカインおよびオピオイドのみを対象としている．残念ながら日本においても，依存性物質誘発症状の包括的な治療ガイドラインは作成されていない．

薬物療法の種類

依存性物質誘発症状の治療は，依存性物質ごとに，急性期解毒，離脱期の治療，精神依存の治療，関連精神障害の治療の段階がある（**表1**）．

アルコール

アルコールの急性期解毒に特異的な治療薬はないが，アルコール排泄の促進に利尿薬が用いられる[3]．アルコール依存では身体依存が強いので，離脱期にはベンゾジアゼピン系薬物などによる薬物療法が重要であり有効である．他の

表1　依存性物質誘発症状のおもな薬物療法

依存性物質	急性期解毒	離脱期の治療
アルコール	利尿薬	ベンゾジアゼピン系薬物，ビタミンB群，葉酸，ニコチン酸
ベンゾジアゼピン系薬物	フルマゼニル	ベンゾジアゼピン系薬物，クロニジン
オピオイド	ナロキソン	ブプレノルフィン，methadone，クロニジン
中枢神経刺激薬	ベンゾジアゼピン系薬物，抗精神病薬，利尿薬	ベンゾジアゼピン系薬物
有機溶剤	抗精神病薬	
ニコチン		ニコチン，バレニクリン

依存性物質に対する依存と同様，精神依存の治療はアルコールの場合もきわめて難しい．日本では，飲酒によって不快感を引き起こさせる抗酒薬が用いられている．欧米では，飲酒欲求を抑制する薬物も用いられている．アルコール依存の治療では，ビタミン製剤の補給も重要である．

ベンゾジアゼピン系薬物

睡眠薬など，γ－アミノ酪酸（γ-aminobutyric acid: GABA）受容体を活性化するベンゾジアゼピン系薬物の場合は，急性期解毒には拮抗薬が用いられ，離脱期にはおもに長期作用型のベンゾジアゼピン系薬物が用いられる[4]．

オピオイド

ヘロインやモルヒネに代表されるオピオイドの場合，急性期解毒には拮抗薬が用いられ，離脱期にはおもにオピオイドが用いられる[2]．精神依存の治療は難しいが，欧米ではオピオイドによる維持療法が行われている．

中枢神経刺激薬

メタンフェタミンは日本で最も乱用が深刻な薬物であり，中枢神経刺激薬依存の治療法の確立が望まれるところであるが，海外も含めて中枢神経刺激薬の精神依存の治療法は確立していない．基礎研究から，さまざまな薬物療法の候補があげられており[5]，今後の展開が待たれるところである．中枢神経刺激薬は，急性および遷延性の精神病症状を引き起こすことが多く，その場合は，ハロペリドール（セレネース®，ケセラン®など）やリスペリドン（リスパダール®）などの抗精神病薬による治療が必要である．

有機溶剤

有機溶剤の場合，重篤な離脱症状が現れることはまれであるが，脳障害などの二次性身体障害が多く認められる[6]．精神病症状には，抗精神病薬が用いられる．

ニコチン

ニコチン依存の場合，離脱期と精神依存の治療として，ニコチンガム（ニコレット®）とニコチンパッチ（ニコチネルTTS®）などのニコチン製剤やバレニクリン（チャンピックス®）が用いられる[7]．ニコチン依存では精神病症状は誘発されないので，関連精神障害としては不

表1　依存性物質誘発症状のおもな薬物療法（続き）

精神依存の治療	関連精神障害の治療
抗酒薬，acamprosate，naltrexone	抗うつ薬（不安，うつ），ビタミン類（器質性脳障害），抗精神病薬（幻覚など）
ベンゾジアゼピン系薬物	
methadone	
抗精神病薬	抗精神病薬（精神病症状），抗うつ薬（不安，うつ）
抗精神病薬，カルバマゼピン	抗精神病薬（精神病症状）
ニコチン，バレニクリン，bupropion	

表2　依存症の薬物療法の分類

薬物療法	治療薬	依存性物質
作動薬療法	methadone，ブプレノルフィン	オピオイド
	ベンゾジアゼピン系薬物	アルコール，ベンゾジアゼピン系薬物
	ニコチン，バレニクリン	ニコチン
拮抗薬療法	naltrexone，ナロキソン	オピオイド
	抗ドパミン薬	中枢神経刺激薬
代謝阻害療法	ジスルフィラム，シアナミド	アルコール
対症療法	クロニジン	オピオイド，ベンゾジアゼピン系薬物（自律神経症状）
	抗精神病薬	中枢神経刺激薬など（精神病症状，渇望感）
	抗うつ薬	アルコール，中枢神経刺激薬など（不安，うつ）

（柳田知司，2000[11]より）

安や焦燥感，うつなどが中心であり，抗うつ薬などが用いられる．ニコチン依存の具体的な治療方法は，「禁煙治療のための標準手順書」[8]に詳しく記載されている．

大麻

大麻依存に対しては，特異的な薬物療法はない[9]．急性期の精神病症状は薬物投与なしで経過観察が基本であるが，強い恐怖感，発汗，動悸などの顕著な自律神経症状がみられた場合は，ジアゼパム（セルシン®，ホリゾン®など）などの穏和精神安定薬を投与する．誇大妄想などの幻覚・妄想や躁性の興奮を伴うときはハロペリドールなどの抗精神病薬を投与する．精神病症状が遷延化する場合があり，これに対しては抗精神病薬の少量長期（1年以上）投与が有効である．

病的賭博

病的賭博など，物質以外への依存の場合，薬物療法は確立していないが，海外では選択的セロトニン再取り込み阻害薬（selective serotonin reuptake inhibitor: SSRI），とくにfluoxetine（prozac®）の使用報告が多い[10]．フルボキサミン，パロキセチン（パキシル®）も使用されており，イミプラミン（イミドール®，クリテミン®，トフラニール®），リチウム（リーマス®），バルプロ酸（デパケン®，セレニカ®など）などの併用も報告されている．このほか，日本では認可されていないnaltrexoneが，病的賭博や自傷行為などに対して衝動を抑制する効果を持つといわれている．ただし，薬物療法のみでは治癒しないことが常に指摘されている．

作用機序による薬物療法の分類

治療段階や問題物質による分類以外に，治療薬の作用機序によって薬物療法を分類することができる[11]（**表2**）．作動薬療法は，依存薬類似の作用を持つ薬物を治療薬として用いる方法であり，依存性物質の代わりに投与することで離脱症状の発現を抑え，また，ある程度の満足感を与えることにより摂取の渇望を減弱させ，断薬を継続させる療法である．ヘロイン依存に対するmethadone療法やベンゾジアゼピン系薬物依存に対するジアゼパム投与などが典型的な作動薬療法である．

拮抗薬療法は，依存性物質の薬理作用を遮断することにより，摂取しても効果を発現させないようにする，あるいは効果を減弱させる治療

薬を用いる療法である．ヘロイン依存に対するnaltrexone投与や中枢神経刺激薬に対する抗精神病薬投与が典型的である．

代謝阻害療法は，依存性物質の中間代謝物の代謝を阻害してその不快な効果を体験させることにより，依存薬と快感との条件づけを依存薬と不快感との条件づけに置き換える療法である．抗酒薬が当てはまる．

対症療法は，依存性物質によって誘発される精神病症状や器質性脳障害などの症状に対する治療法である．精神病症状には統合失調症に対してと同様の治療がなされる．

急性期解毒の薬物療法

急性中毒が疑われる患者には，心肺機能や意識障害を確認し，必要に応じて救命処置を講ずる[12,13]．同伴者からの情報，臨床所見，薬物スクリーニング検査などにより薬物の種類，摂取量，摂取経路を同定する．6時間以内の経口摂取の場合は，胃洗浄や活性炭の使用を考慮する．アルカリ化か酸性化かに注意し，利尿薬を投与して，薬物の排泄を促進する（バルビツール酸系薬物の排泄には尿をアルカリ化し，メタンフェタミンの排泄には尿を酸性化する）．比較的軽症な例では，精神運動興奮，傷害，自殺企図などの異常行動に対する対応が治療の中心となる．興奮や暴力行為の著しい患者には，全身状態に注意しながら，ハロペリドールなどの抗精神病薬やジアゼパムなどを投与して鎮静を図る．ベンゾジアゼピン系薬物の過量服用には拮抗薬のフルマゼニル（フルマゼニル®），オピオイドによる呼吸抑制などにはナロキソンでそれぞれ対応する．中枢神経刺激薬による異常興奮にはベンゾジアゼピン系薬物や抗精神病薬によって鎮静させる．有機溶剤による異常興奮の場合も抗精神病薬を用いる．大麻やタバコの場合は，急性期解毒に薬物療法を要する場合はまれである．

離脱期の薬物療法

アルコール依存

アルコールの離脱期には，交差耐性のあるベンゾジアゼピン系薬物がおもに用いられる[14]．これは，アルコールがベンゾジアゼピン系薬物の標的であるGABA受容体に作用するためと考えられる．治療には，ジアゼパムなどの長期作用型で力価の低いベンゾジアゼピン系薬物を用い，漸減する．漸減の仕方は，1～2週間で投与量を1/2として，4～8週間以上かけて治療薬投与を終了させる．高齢者や肝機能障害患者，器質性脳障害患者など，長期作用型ベンゾジアゼピン系薬物による過鎮静のリスクが考えられる場合は，ロラゼパム（ワイパックス®）などの中期作用型の薬物を用いるが，アルコールと治療薬の離脱が重ならないように注意が必要である．また，離脱症状が強い場合は，振戦せん妄を防ぐためにブロマゼパム（レキソタン®など）などの高力価のベンゾジアゼピン系薬物を用いるが，依存の危険があるので長期間の投与にならないように注意が必要である．

自律神経症状（ノルアドレナリン神経系の異常亢進）が激しい場合は，クロニジン（カタプレス®）やプロプラノロール（インデラル®）などを用いてノルアドレナリン神経伝達を減弱させる．クロニジンはシナプス前部にあるα_2アドレナリン受容体に作用して，ノルアドレナリンの放出を抑制する．プロプラノロールはβ遮