●研修速報●　［既刊号の案内］

年・月		
11・7	第300号	法医学研修第3弾 DNA鑑定の基礎について
7	第301号	平成22年度　倒産手続実務・基礎研修 第1回「破産同時廃止手続申立」
7	第302号	平成22年度　倒産手続実務・基礎研修 第3回「破産管財手続申立」
7	第303号	国際ライセンス契約の実務
7	第304号	「これでいいのか裁判員裁判」 ―より実りある弁護活動を行うために―
8	第305号	公判前整理手続・裁判員制度の改革課題 平成22年度行政専門弁護士養成講座
8	第306号	第9シリーズ　第1回「景観法の意義と到達点」 平成22年度行政専門弁護士養成講座 第9シリーズ　第2回「地方自治体経営と弁護士」 ～法曹との連携によるコンプライアンスの徹底～
8	第307号	破産管財人の源泉徴収義務に関する研修会
8	第308号	労働問題基礎講座【第2回】 「解雇・有期雇用」―解雇・雇止め等をめぐる問題―
8	第309号	労働問題基礎講座【第3回】 「労働基準法改正・労働時間問題」
8	第310号	労働問題基礎講座【第4回】 「労災・過労自殺」
8	第311号	脳外傷の画像による鑑別診断 ―画像で脳外傷はどこまで判明するか　mTBIを中心として―
8	第312号	医療問題連続講座(第1回) 入院していても学びたい　～病弱教育の現状と課題～
8	第313号	医療問題連続講座(第2回) 医療を受ける子どもの人権　～何が問題か～

年・月		
11・8	第314号	改正土壌汚染対策法と瑕疵担保責任 ①土壌汚染と瑕疵担保責任 ―平成二二年六月一日最高裁判決を踏まえて― ②土壌汚染とリーガルリスク ③改正土壌汚染対策法と鑑定評価
8	第315号	包括外部監査人補助者推薦弁護士名簿登録研修　第2回 地方財政法、地方財政健全化法の基礎知識
8	第316号	憲法問題連続学習会（第39回） 「ドイツ政治と選挙制度 ―デモクラシーの空洞化に高まる政治不信」
8	第317号	最近の個人情報保護を巡る諸問題について
9	第318号	憲法問題連続学習会（第40回） 「在日米軍地位協定の概要と問題点」
9	第319号	憲法問題連続学習会（第41回） 「国際法から見た日本の領土問題」
9	第320号	医療問題連続講座（第3回） 患者の権利について ～これまでとこれから～
9	第321号	中小企業における『私的整理』の現状とあり方
9	第322号	CRPS 複合性局所疼痛症候群について

※印は売切れです。
第1号から第299号に関しましては、お問い合わせ下さい。

4）神経障害性疼痛（神経障害痛）とその治療

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key words　neuropathic pain, IASP, guideline, pharmacotherapy, algorithm

要　旨

神経障害性疼痛（神経障害痛）は，2008年IASP（世界疼痛学会）により，“体性感覚系に対する損傷や疾患によって直接的に引き起こされる疼痛”と定義されている．先進国の神経障害性疼痛の罹患率は1～7%と推定されており，本邦では数百万人程度の神経障害性疼痛患者の存在が推測されている．様々な疾患・病態が含まれているが，神経損傷部位により末梢性と中枢性に分けて分類されることが多い．痛みの臨床的特徴は共通したものが多く，その病態には共通点があると予測される．診断には，診断基準やアルゴリズム，スクリーニングツール（簡易調査票）が用いられる．治療には，薬物治療の他に，外科的療法，神経ブロック，脊髄刺激療法，理学療法，心理療法などがある．適切な薬物療法を行っても十分な鎮痛効果が得られない症例も多くあり，この場合多岐にわたる非薬物治療や侵襲的治療が必要なため，可及的速やかに“痛み治療の専門医”に紹介することが望ましい．

A. 神経障害性疼痛とは

神経障害性疼痛（神経障害痛）は1990年代に初めて一般的に用いられるようになった用語である．IASPは1990年に神経障害性疼痛を“神経系の一時的な損傷，あるいはその機能異常が原因となって生じた痛み”と定義した[1]．しかしこの定義は，神経障害性疼痛と侵害受容性疼痛の特徴を見分けるのには有用性が高いが，診断の特異性や解剖学的正確性に欠けているなどあいまいな点が多いため，2008年，IASPは，この定義を，“体性感覚系に対する損傷や疾患によって直接的に引き起こされる疼痛”と変更した[2]．疼痛疾患の中ではその重症度が高く罹病期間も長いため患者の著しいQOL（quality of life）とADL（activities of daily living）の低下をもたらす[3,4]．最近のデータで，先進国の神経障害性疼痛の罹患率は1～7%と推定されており[3,5]，本邦では数百万人程度の神経障害性疼痛患者が存在していると推測される．

B. 神経障害性疼痛の分類と診断

神経障害性疼痛には様々な疾患が含まれているが，神経損傷部位により末梢性と中枢性に分けて分類されることが多い（表1）[4]．神経障害性疼痛の痛みの臨床的特徴は共通したものが多く（表2）[6]，知覚異常，痛みの質，痛みの強弱，痛みの発現する時間的パターンなどからみて，その病態には共

表1　神経障害性疼痛に包括される一般的な疾患・病態（神経損傷部位による分類）（文献4より引用改変）

神経障害性疼痛	
末梢性神経障害性疼痛	中枢性神経障害性疼痛
・帯状疱疹後神経痛	・脳卒中後疼痛
・有痛性糖尿病性神経障害	・外傷性脊髄損傷後疼痛
・複合性局所疼痛症候群	・多発性硬化症による痛み
・化学療法による神経障害	・脊柱管狭窄による圧迫性脊髄症
・HIV感覚神経障害	・パーキンソン病に伴う痛み
・幻肢痛*	・HIV脊髄症
・三叉神経痛	・虚血後脊髄症
・急性/慢性炎症性の脱髄性多発神経根障害	・放射線照射後脊髄症/放射線照射後脳症
・アルコール性神経障害	・脊髄空洞症/延髄空洞症
・絞扼性末梢神経障害（手根管症候群など）	
・医原性神経障害（乳房切除術後疼痛，開胸術後疼痛など）	
・特発性感覚性神経障害	
・腫瘍による神経圧迫または浸潤による神経障害*	
・栄養障害による神経障害	
・放射線照射後神経叢障害*	
・神経根障害	
・中毒性末梢神経障害	
・外傷性末梢神経損傷後疼痛	
・腕神経叢引き抜き損傷*	
・舌咽神経痛	
・自己免疫性神経障害*	
・慢性馬尾障害*	

*末梢性および中枢性神経障害性疼痛の両方に当てはまる可能性がある．

表2　神経障害性疼痛の臨床的特徴[6]

①知覚異常：自発痛と刺激で誘発される痛みの両者もしくはそのどちらか．
　痛覚過敏（hyperalgesia），アロディニア（allodynia），
　感覚異常（paresthesia），異常感覚（dysesthesia），
　無知覚（loss of sensation）や知覚低下（imperception）の場合もある．
　感覚鈍麻（hypesthesia），痛覚鈍麻（hypoalgesia），
　温覚鈍麻（thermhypesthesia），振動覚鈍麻（pallhypesthesia）

②痛みの質
　電撃痛（lancinating pain or shooting pain），
　刺すような痛み（stabbing），灼熱痛（burning pain），鈍痛（dull pain），
　うずく痛み（aching pain），拍動痛（pulsatile pain）

③痛みの強弱

表3　神経障害性疼痛の臨床的分類のための診断基準（文献7より引用一部改変）

●確実な (definite): 痛みが神経解剖学的部位に局在しており，少なくとも次の診断基準のうち2つを満たす．
①疼痛部位のすべてもしくは一部に知覚低下がある
②この痛みに関連する神経病変（障害）を引き起こすことが知られている疾患が，現在もしくは今までにある
③神経生理学，外科もしくは神経映像化により確認された神経病変（障害）がある

●可能性のある (possible): 痛みが神経解剖学的部位に局在しており，少なくとも次の診断基準のうち2つを満たす．
①疼痛部位のすべてもしくは一部に知覚低下がある
②病因不明*
③この痛みに関連する侵害受容性疼痛もしくは神経障害性疼痛のどちらかを引き起こすことが知られている疾患が，現在もしくは今までにある
④放散痛もしくは発作痛がある

●可能性が薄い (unlikely): 痛みが少なくとも次の診断基準のうち2つを満たす．
①痛みが神経解剖学的部位でないところにある
②痛みの部位に侵害受容性疼痛を引き起こすことが知られている疾患が，現在もしくは今までにある
③知覚低下がない

*知られていない疾患もしくは病変

表4　わが国における神経障害性疼痛のグレード（等級）分類とその診断に必要な診断基準（文献8より引用）

●確実な (definite): 痛みが神経解剖学的部位に局在しており，少なくとも次の診断基準のうち3つを満たす．
①疼痛部位のすべてもしくは一部に知覚低下がある
②疼痛部位のすべてもしくは一部にアロディニア，知覚過敏，痛覚過敏がある
③この痛みに関連する神経病変（障害）を引き起こすことが知られている疾患が，現在もしくは今までにある
④神経生理学，外科もしくは神経映像化により確認された神経病変（障害）がある

●可能性が高い (highly possible): 痛みが神経解剖学的部位に局在しており，少なくとも次の診断基準のうち3つを満たす．
①疼痛部位のすべてもしくは一部に知覚低下がある
②疼痛部位のすべてもしくは一部にアロディニア，知覚過敏，痛覚過敏がある
③病因不明
④この痛みに関連する侵害受容性疼痛もしくは神経障害性疼痛のどちらかを引き起こすことが知られている疾患が，現在もしくは今までにある
⑤放散痛もしくは発作痛がある

●可能性が薄い (unlikely): 痛みが少なくとも次の診断基準のうち3つを満たす．
①痛みが神経解剖学的部位でないところにある
②痛みの部位に侵害受容性疼痛を引き起こすことが知られている疾患が，現在もしくは今までにある
③知覚低下がない
④知覚過敏がない

通点があると予測される．

診断には，臨床的分類やグレード分類のための診断基準がしばしば用いられる（表3，表4）[7,8]．また主訴，現症と病歴，評価・検査から段階的な評価で診断するアルゴリズムも簡便で有効性が高い（図1）[7]．本邦では，ペインクリニック専門認定施設14施設からなる神経障害性疼痛スクリーニング研究会によるスクリーニングツール（簡易調査票）が開発され，高い診断感度が評価されている（図2）[9]．

C．神経障害性疼痛の治療

神経障害性疼痛に包含されるさまざまな疾患（表1）のそれぞれに対する多様な治療法を個々にすべて記すことは困難である．この項では，神経障害性疼痛全般に対する薬物治療についてのみ記すこととする．実際の神経障害性疼痛に対する治療には，薬物治療の他に，外科的療法，神経ブロック，脊髄刺激療法，理学療法，心理療法などがあるが詳細は成書を参照されたい[10]．

D．薬物治療

神経障害性疼痛は，非ステロイド性消炎鎮痛薬（NSAIDs）やオピオイドなどの既存の鎮痛薬の効果が不十分なことや，神経障害性疼痛に有効とされる鎮痛薬であっても単独での効果が少なく，多剤を併用しなければならないことも多く，また鎮痛効果の発現までに数日を要することもあり，その使用方法は単純ではない．さらに重篤なものを含めた副作用も多く，薬物治療にはかなりの知識と経験を要する．このため，海外では，神経障害性疼痛に対する薬物治療の簡便化と安全性向上のため多くのガイドラインが出版されている[11,12]．本邦においても日本ペインクリニック学会や日本疼痛学会を中心に本邦の医療環境に応じたevidence-based medicine（EBM）に則った神経障害性疼痛薬物療法ガイドラインが間もなく上梓される予定であり[13]，神経障害性疼痛患者のQOL

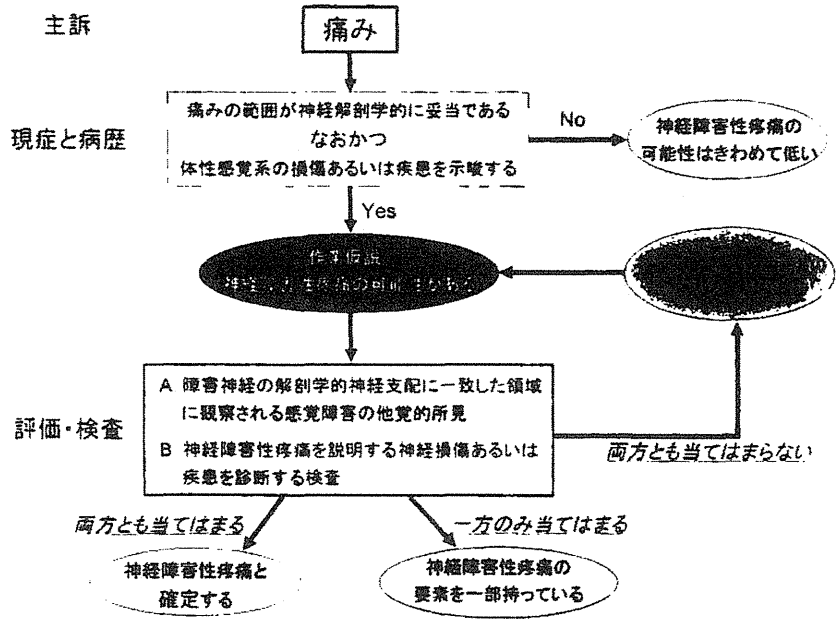
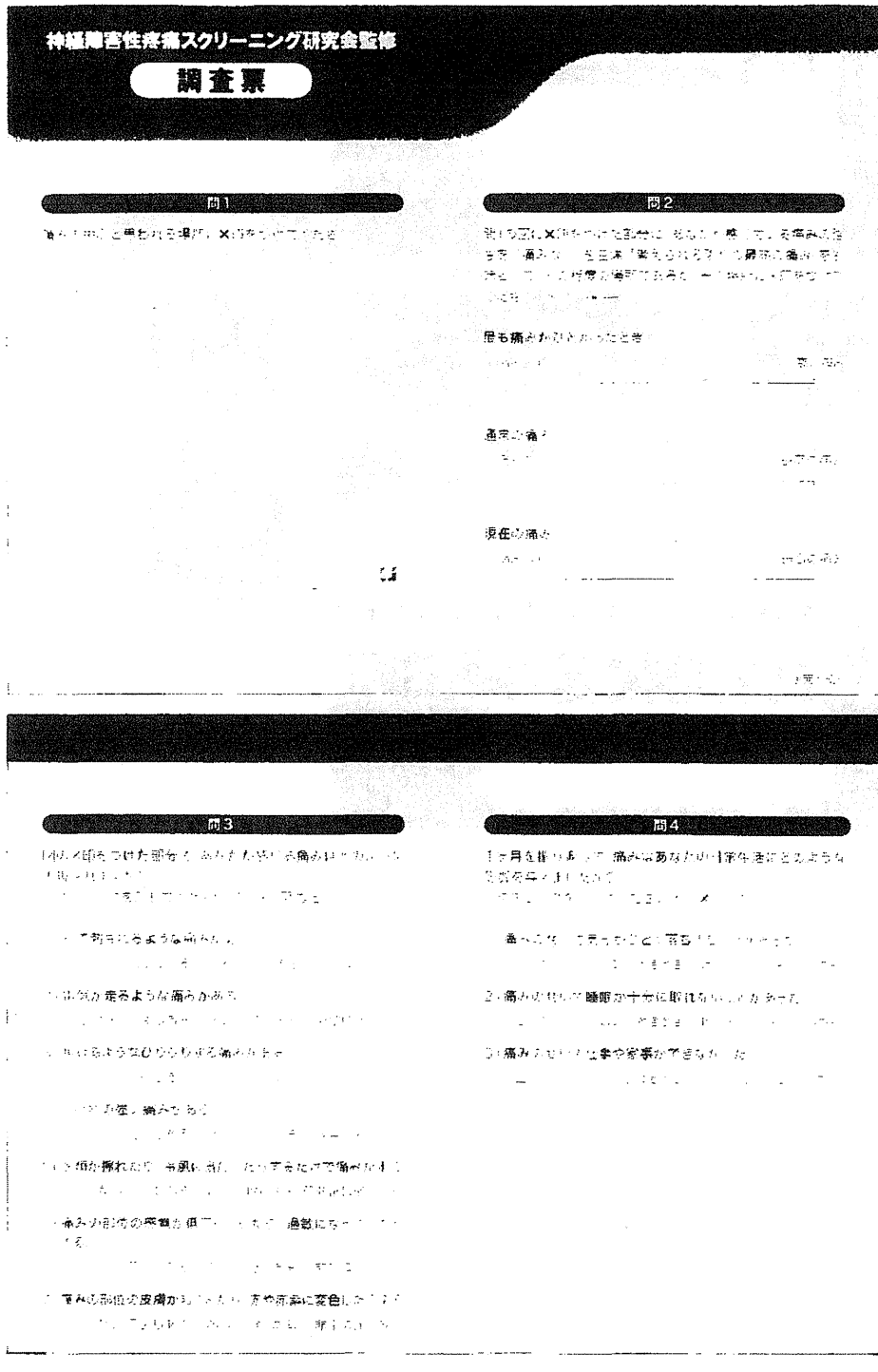


図1　神経障害性疼痛診断アルゴリズム（文献7より引用，一部を改変）


神経障害性疼痛スクリーニング研究会監修

調査票

問1

問2

問3

問4

図2　簡易調査票[1]

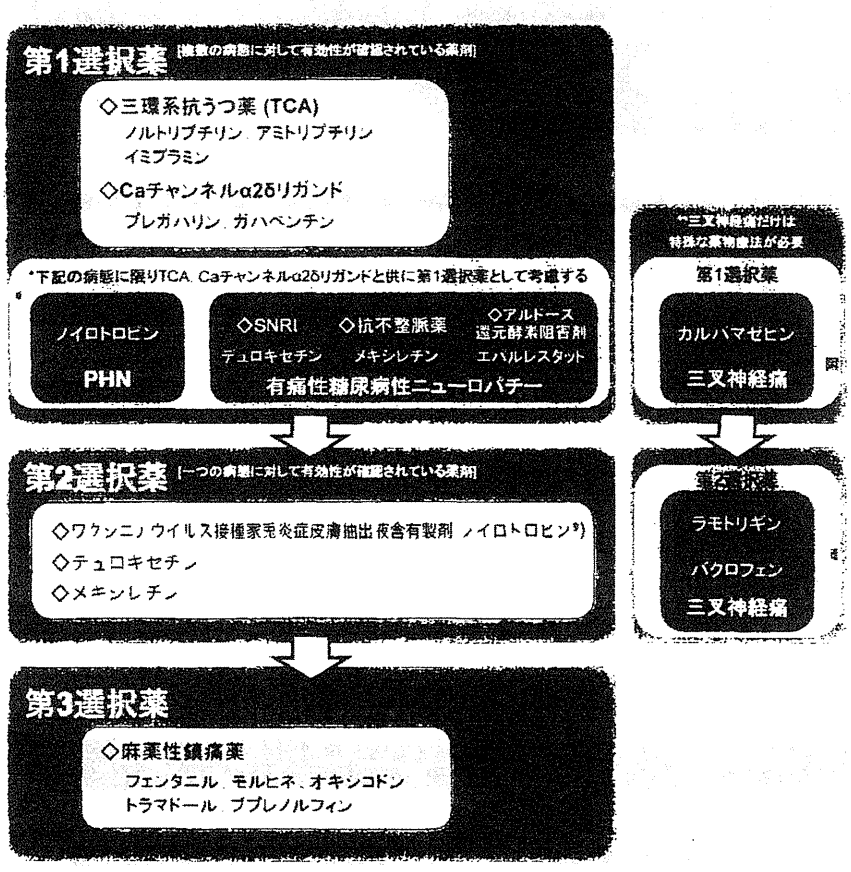


図3　本邦における神経障害性疼痛薬物療法アルゴリズム（文献13より引用）
PHN＝帯状疱疹後神経痛，SNRI＝セロトニン・ノルアドレナリン再取り込み阻害薬

向上に寄与することが期待されている．海外，本邦（図3）ともにガイドラインでは，第1選択薬，第2選択薬，第3選択薬というようにアルゴリズムに沿って薬剤を順次選択していくことを推奨している．ここでは，その選択順に従って，説明を加える．

1．第1選択薬

a．三環系抗うつ薬

三環系抗うつ薬 tricyclic antidepressant（TCA）に関しては，プラセボに比した有意な鎮痛効果があり[14,15]，抗うつ作用とは無関係に鎮痛作用を有する．セロトニンおよびノルアドレナリンの再取り込み阻害のバランスが取れた第三級アミンTCA（アミトリプチリン塩酸塩，イミプラミン塩酸塩）とノルアドレナリン取り込みの比較的選択的な阻害を有する第二級アミンTCA（ノルトリプチリン塩酸塩）との間で，鎮痛効果に差はなく[16]，副作用が少ないという理由から，第二級アミンTCA（ノルトリプチリン塩酸塩およびデシプラミン）が好ましい．特に高齢者の場合，アミトリプチリン塩酸塩の使用は低用量から開始し，慎重に使用する[17]．

b．カルシウムチャネル$\alpha_2\delta$リガンド

ガバペンチン（ガバペン®）とプレガバリン（リリカ®）は中枢神経系において，カルシウムチャネルの$\alpha_2\delta$サブユニットと結合することにより興奮性神経伝達物質の遊離を抑制し鎮痛に働く．

両者は類縁化合物であり同様の作用がある．ガバペンチンは海外では神経障害性疼痛に対して有効性が示されているが本邦では保険適応がない．プレガバリンは，国内および海外で帯状疱疹後神経痛[18-20]，糖尿病性ニューロパチー[21-24]を始めとする末梢性神経障害性疼痛に伴う痛みとしびれに対して，また神経根症に対しても[25]鎮痛効果があり，睡眠の質についても改善することが示されている．腎機能低下患者には投与量を減量する必要があることと，眠気，ふらつきが高齢者に発現するため，低用量の投与で開始するなど注意が必要である[11]．

2. 第2選択薬

a. 本邦の特異的な治療薬：ワクシニアウイルス接種家兎炎症皮膚抽出液含有製剤（ノイロトロピン®）

ワクシニアウイルス接種家兎炎症皮膚抽出液含有製剤（ノイロトロピン®）は，帯状疱疹後神経痛に，その鎮痛効果が示されている[26]．重篤な副作用がなく安全性が高い[26,27]．

b. セロトニン・ノルアドレナリン再取り込み阻害薬（serotonin noradrenalin reuptake inhibitor (SNRI)）

セロトニン・ノルアドレナリン再取り込み阻害薬（SNRI，デュロキセチン塩酸塩）はTCAに比して安全で使用しやすい．鎮痛機序は下行性疼痛抑制系の賦活と考えられている．デュロキセチンは糖尿病性ニューロパチーによる痛みとしびれへの効果が確認されている[28,29]．

c. 抗不整脈薬

メキシレチン塩酸塩は抗不整脈薬であり，作用機序はナトリウムチャネル遮断である．本邦では，有痛性糖尿病性ニューロパチー，特に急性の自発痛に対する鎮痛効果があるとされている[30]．

3. 第3選択薬：麻薬性鎮痛薬（医療用麻薬）および弱オピオイド製剤

フェンタニル経皮吸収型製剤[31]，オキシコドン[32,33]，モルヒネ[34,35]，ブプレノルフィン塩酸塩[36]などの麻薬性鎮痛薬の神経障害性疼痛に対する鎮痛効果が示されている．しかし，本邦では緩和ケア領域以外での麻薬性鎮痛薬の使用にあたって十分な経験が蓄積されていない．このため，開始前の乱用のリスクファクターを特定することや投与後の治療効果判定ともに乱用，嗜癖の徴候について定期的な評価を繰り返し行うことなどが重要となる[37]．麻薬性鎮痛薬は副作用の発現頻度が高く，副作用が治療期間全般を通じて長期に渡って継続する可能性がある[38]ことや麻薬性鎮痛薬の長期安全性に関して体系化された検討が行われておらず，麻薬性鎮痛薬が他の薬物よりも本質的に安全性が高いとは言い切れないことなども含め，安易な使用は慎まなければならない．麻薬性鎮痛薬の維持量はモルヒネ換算15～120mg/日が推奨されており，それ以上を必要とする場合には“痛み治療の専門医”に相談するべきである．

トラマドール塩酸塩製剤（トラマール®）は，現在，がん疼痛に本邦でも使用されている．オピオイド同様にμ-受容体に作用するが，5-HT，NA再吸収阻害作用もあり，副作用がオピオイドに比べ少ないことから，神経障害性疼痛に対しての，効果が期待されている[39,40]．

4. その他

第1選択薬，第2選択薬，第3選択薬に反応を示さなかった場合，以下の薬剤の使用も選択となるがその適応は限られる．抗けいれん薬であるカルバマゼピン，バルプロ酸ナトリウム，ラモトリギン，トピラマート，NMDA受容体拮抗薬であるケタラール，デキストロメトルファン臭化水素酸塩製剤，ビタミンB_{12}製剤であるメコバラミンなどがある．

むすび

神経障害性疼痛の治療は薬物治療のみではない．適切な薬物療法を行っても十分な鎮痛効果が得られない症例もある．鎮痛が得られない場合には多岐にわたる非薬物治療や侵襲的治療が必要であり，また有効な場合がある．こういった症例は可及的速やかに痛み治療の専門医に紹介することが望ましい．

文献

1) Merskey H, et al. Classification of chronic pain. 2nd ed. Seatle: IASP Press; 1994. p.207.
2) Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. Pain. 2008; 137: 473-7.
3) Bouhassira D, Lanteri-Minet M, Attal N, et al. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain. 2008; 136: 380-7.
4) Melzak R, Katz J. Pain assessment in adult patients. In: Wall PD, Melzak R, editors.Textbook of Pain. Edinburg: Churchill Livingstone; 2008. p.291-316.
5) Gilron I, Watson CP, Cahill CM, et al. Neuropathic pain: a practical guide for the clinician. CMAJ. 2006; 175: 265-75.
6) 細川豊史．定義と臨床的特徴．In: 小川節郎，編．神経障害性疼痛治療ガイドブック．東京: 南山堂; 2010. p.2-4.
7) Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008; 70: 1630-5.
8) 細川豊史．分類．In: 小川節郎，編．神経障害性疼痛治療ガイドブック．東京: 南山堂; 2010. p.5-9.
9) 小川節郎．日本人慢性疼痛患者における神経障害性疼痛スクリーニングツール質問表の開発．ペインクリニック．2010; 31: 1187-94.
10) 住谷昌彦，齋藤洋一，信太賢治，他．第3治療 3-6項．In: 小川節郎，編．神経障害性疼痛治療ガイドブック．東京: 南山堂; 2010. p.86-114.
11) Dworking RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. Pain. 2007; 132: 237-51.
12) Attal N, Cruccu G, Haanpaa M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol. 2006; 13: 1153-69.
13) 神経障害性疼痛に対する薬物療法ガイドライン．日本ペインクリニック学会誌．投稿中．
14) Bowsher D. The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. J Pain Symptom Manage. 1997; 13: 327-31.
15) Rintala DH, Holmes SA, Courtade D, et al. Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. Arch Phys Med Rehabil. 2007; 88: 1547-60.
16) Sindrup SH, Bach FW, Madsen C, et al. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology. 2003; 60: 1284-9.
17) Watson CPN, Vernich L, Chipman M, et al. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. Neurology. 1998; 51: 1166-71.
18) Sabatowski R, Galvez R, Cherry DA, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. Pain. 2004; 109: 26-35.
19) Dworkin RH, Corbin AE, Young JP, Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology. 2003; 60: 1274-83.
20) Stacey BR, Barrett JA, Whalen E, et al. Pregabalin for postherpetic neuralgia: placebo-controlled trial of fixed and flexible dosing regimens on allodynia and time to onset of pain relief. J Pain. 2008; 9: 1006-17.
21) Arezzo JC, Rosenstock J, Lamoreaux L, et al. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double blind placebo-controlled trial. BMC Neurol. 2008; 8: 33.
22) Rosenstock J, Tuchman M, Lamoreaux L, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain. 2004; 110: 628-38.

23) Tolle T, Freynhagen R, Versavel M, et al. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: A randomized, double-blind study. Eur J Pain. 2008; 12: 203-13.
24) Freeman R, Durso-DeCruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. Diabetes Care. 2008; 31: 1448-54.
25) Saldaña MT, Navarro A, Pérez C, et al. Patient-reported-outcomes in subjects with painful lumbar or cervical radiculopathy treated with pregabalin: evidence from medical practice in primary care settings. Rheumatol Int. 2010; 30: 1005-15.
26) 山村秀夫, 檀健二郎, 若杉文吉, 他. ノイロトロピン錠の帯状疱疹後神経痛に対する効果 プラセボ錠を対照薬とした多施設二重盲検試験. 医学のあゆみ. 1988; 147: 651-64.
27) 祖父江逸郎, 花籠良一, 松本昭久, 他. SMON (subacute myelo-optico-neuropathy) 後遺症に対するノイロトロピンの臨床評価 多施設二重盲検交差比較試験. 医学のあゆみ. 1987; 143: 233-52.
28) Goldstein DJ, Lu Y, Detke MJ et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain. 2005; 116: 109-18.
29) Wernicke JF, Pritchett YL, D'Souza DN et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology. 2006; 67: 1411-20.
30) Nishizawa Y, Yoshioka F, et al. Improving and Protecting Effect and Safety of Mexiletine Hydrochloride or Mianserin Hydrochloride on Painful Diabetic Neuropathy in Patients with Type 2 Diabetes Mellitus for 2 years in Prospective Randomized Well-controlled Comparative Study. 慢性疼痛. 2005; 24: 137-48.
31) 宮崎東洋, 花岡一雄, 並木昭義, 他. デュロテップ®MTパッチの非癌性慢性疼痛患者を対象とした臨床試験 I : 4週および長期 (52週) 貼付. 新薬と臨床. 2010; 59: 157-80.
32) Watson CPN, Babul N. Efficacy of oxycodone in neuropathic pain: A radomized trial in post-herpetic neuralgia. Neurology 1998; 50: 1837-41.
33) Watson CPN, Moulin D, Watt-Watson J, et al. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain. 2003; 105: 71-8.
34) Agarwal S, Tella PK et al. Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. Anesthesiology. 2008; 109: 289-96.
35) Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005; 352: 1324-34.
36) Rowbotham MC, Twilling L, Davies PS, et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med. 2003; 348: 1223-32.
37) Hojsted J, Sjogren P. Addiction to opioids in chronic pain patients: a literature review. Eur J Pain. 2007; 11: 490-518.
38) Watson CPN, Watt-Watson JH, Chipman ML. Chronic non-cancer pain and the long term utility of opioids. Pain Res Manage. 2004; 9: 19-24
39) Arbaiza D, Vidal O. Tramadol in the treatment of neuropathic cancer pain: a double-blind, placebo-controlled study. Clin Drug Investig. 2007; 27: 75-83.
40) Boureau F, Legallicier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. Pain. 2003; 104: 323-31.

2

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	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