

Clinical Challenges: Chemotherapy-Induced Peripheral Neuropathy

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Disclosure

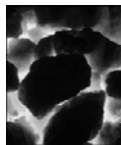
■ Advisory Board/Consultant

- Abbott
- Alpharma
- Dendreon
- GW
- Valeant

Chemotherapy Induced Peripheral Neuropathy



■ Discuss the challenge of treating pain and altered sensations associated with chemotherapy-induced peripheral neuropathy



Common Neuropathic Pain Syndromes in Cancer

- Paraneoplastic sensorimotor neuropathy
- Postherpetic neuropathy
- Post-radiation plexopathies
- Surgical neuropathies
 - Phantom pain
 - Post-mastectomy syndrome
 - Post-thoracotomy syndrome

Common Neuropathic Pain Syndromes in Cancer

- Brachial plexus neuropathies
- Cachexia
- Cranial neuropathies
- Chemotherapy-induced neuropathy
 - Bortezomib
 - Cisplatin
 - Oxaliplatin
 - Paclitaxel
 - Thalidomide
 - Vinblastine
 - Vincristine

Non-Cancer-Related Causes of Neuropathies

- Alcohol
- Atherosclerotic ischemia disease
- Diabetes mellitus
- HIV
 - Viral involvement
 - HAART
- Vitamin deficiencies

Challenges in Understanding CI Peripheral Neuropathy

- Neurobiology poorly understood
- Prevalence unclear
- Terminology inconsistent
 - Neuropathy vs. pain
- Lack of standardized assessment
- Absence of gold standard staging system

Neurobiology of CIPN

- Mitochondrial dysfunction – swollen and vacuolated in C and A fibers (sensory neurons)
- ATF3 normal
- Paclitaxel 2 mg/kg injected ip days 0,2,4,6
- Largest sensory neurons of longest length damaged
- Increase in ATF3
- 18 mg/kg iv days 0 and 3

Flatters & Bennett, Pain, 2006

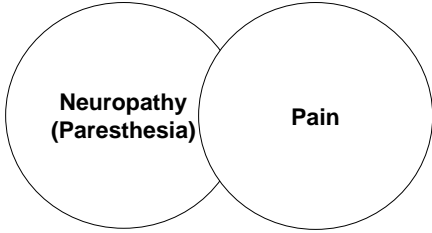
Jimenez-Andrade, et al. Neuroscience Letters, 2006

Prevalence Unclear

- Most studies employ self-report
- Only grade 3 or 4 reported
- Regimen may include more than one potentially toxic agent
- Comorbid conditions rarely recorded
- Time course unknown, including resolution of symptoms

Hausheer FH, et al Semin Oncology 33:15-49, 2006

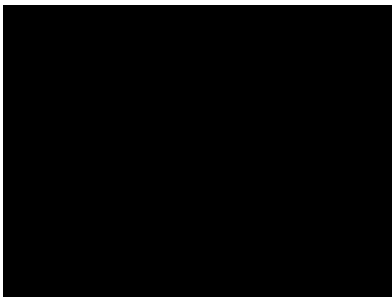
Unclear Terminology



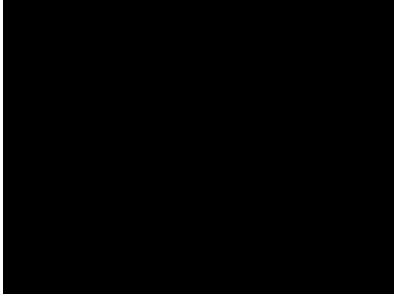
Quality: "Razorblades"



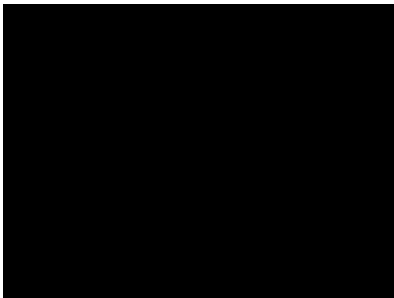
Functional Changes: "Holding Baby"



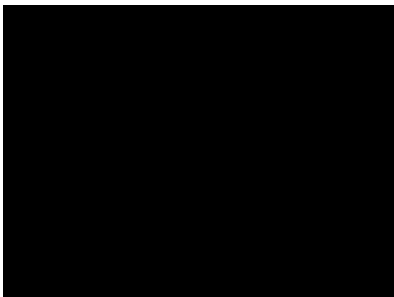
Functional Changes:
Proprioception



Sensory/motor Changes: Coin
Pickup



Proprioception



Lack of Standardized Assessment

- Most existing tools designed to measure PN in diabetes, other conditions
- Few tools for CIPN validated
- Sensation vs. interference (e.g. buttons)
- FACT-Taxane only tool that includes QOL

Hausheer FH, et al Semin Oncology 33:15-49, 2006

Assessment Not Standardized

Tool	Validity	Language	Domains
NPS	DN, PHN, CRPS	36+	Burning Sharp
FACT-Taxane	Extensive in cancer	45+	Numbness ADL limitations
EORTC QLQ CIPN20	Underway	English, French, Dutch	Tingling, numbness, pain, ADL limitations
CIPNS-32	Ovarian cancer	English	Paresthesias, numbness

Assessment Not Standardized

- Descriptors Used in Paclitaxel-Induced Peripheral Neuropathy
 - Numb (100%)
 - Tingling
 - Cold
 - Burning
 - Dull

Dougherty PM. Pain 109:132-142, 2004

QST Not Standardized

	Tests	Findings
Chaudhry <i>Ann Neurol</i> , 1994	Neuro exam Electrophysiology	76% developed paresthesias; EP sural nerve amplitude ↓
Forsyth <i>J Neuro Onc</i> , 1997	Thermal and vibration thresholds	84% developed PN Vibration most sensitive
Dougherty <i>Pain</i> , 2004	Thermal, touch, sharp	Touch and sharp most impaired; Cold sensitive, heat not
Argyriou, <i>Support Care Cancer</i> , 2005	Neuro exam Electrophysiology	Sural nerve EP predictive

Grading Scales for Neuropathy

Scale	Grade 1	Grade 2	Grade 3	Grade 4
NCI-CTCAE ■ Sensory ■ Motor	No symptoms, loss of DTR	Paresthesia, ADL ok	Paresthesia, ADL interference	Disabling
ECOG ■ Sensory ■ Motor	Mild Paresthesia Loss DTR	Sensory loss Paresthesia Weakness	Severe sensory and motor loss with function	Paralysis
WHO	Paresthesia Decreased DTR	Severe paresthesia Weakness	Intolerable	Paralysis

Postma T.J. *Annals Oncol* 9:739-744, 1998

Goals of Treatment

- Prevention
- Decrease pain
- Promote safety

Prophylactic Agents: Preclinical

- Acetyl-L-carnitine (prevention)
 - Flatters, Xiao, Bennett. *Neuroscience Letters* 2006;397:219-223
- Ethosuximide (treatment)
 - Flatters & Bennett. *Pain* 2004;109:150-161

Neuromodulatory Agents Investigated as Prophylaxis or Treatment of Chemo-Induced Neurotoxicity

Study	Agent	Patients Treated (Controls)	Controlled Trial
Penz et al 2001	Amifostine	15	No
Eckel et al 2002	Carbamazepine	10 (30)	No
Gedlicka et al 2002	α -Lipoic acid	15	No
Cascinu et al 2002	Glutathione +	26 (26)	Yes*
Durand et al 2003	Venlafaxine	10	No
Marshall et al 2004	Gingko biloba	17	No

Grothey A. *Clin Colorectal Cancer* 2005; Suppl 1:S38-S46

Neuromodulatory Agents Investigated as Prophylaxis or Treatment of Chemo-Induced Neurotoxicity

Study	Agent	Patients Treated (Controls)	Controlled Trial
Mariani et al 2000	Gabapentin	15	No
Mitchelli et al 2006	Gabapentin	41	No
Gameline et al 2004	Ca ₂ + Mg ₂ Infusion +	96 (65)	Yes*
Argyriou et al 2005	Vitamin E +	16 (15)	Yes*
Cassidy et al 2006	Xaliproden +	324 (325)	Yes

Grothey A. *Clin Colorectal Cancer* 2005; Suppl 1:S38-S46

Novel Compounds: Prevention and Treatment

- **Xaliproden** - Susman E, *Lancet Oncology*, 2006
 - Nonpeptide neurotrophic
 - 5HT 1A agonist
 - Reduced risk grade 3 by 39% FOLFOX
- **L Carnitine** - Flatters, Xiao, Bennett, *Neuroscience Letters* 2006
 - Oxidation of free fatty acids
- **Ethosuximide** - Flatters & Bennet, *J Pain*, 2006
 - Antiseizure, T type Ca channels
- **D-cycloserine**

Oxaliplatin Neurotoxicity: Prevention

- **OPTIMOX**
- **FOLFOX7 x 6 cycles**
- Oxaliplatin held at 780 mg/m², then reintroduced at 6 months or with progressive disease
- Difference in neuropathy not statistically significantly when compared to FOLFOX4

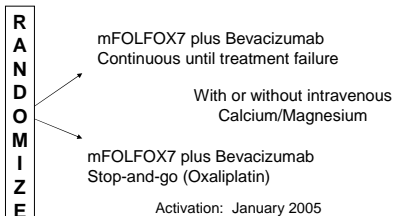
de Gramont A, et al. *Proc ASCO* 2004;23:251.

CONcePT: Combined Oxaliplatin Neurotoxicity Prevention Trial

First-line treatment of metastatic CRC (N = 532)

Primary Endpoint: time to treatment failure

2 x 2 randomization



Grothey A. *Clin Colorectal Cancer* 2005; Suppl 1:S38-S46

Pharmacologic Management

- Nonopioids
- Opioids
- Adjuvant analgesics

Opioids for Neuropathic Pain

- Opioids block the release of neurotransmitters in the spinal cord
- Mu μ , Delta δ , Kappa κ
- Effective for neuropathic pain

Rowbotham M et al; *NEJM* 2003; 348:1223-1232

Opioids

- | | |
|-----------------|---------------|
| ■ Codeine | ■ Methadone |
| ■ Fentanyl | ■ Morphine |
| ■ Hydrocodone | ■ Oxycodone |
| ■ Hydromorphone | ■ Oxymorphone |

Adjuvant Analgesics

- Corticosteroids
- Anticonvulsants
- Tricyclic antidepressants
- Local anesthetics
- Anticancer therapies

Corticosteroids

- Dexamethasone has least mineralocorticoid effect
- All can produce glucocorticoid effects
- Can be given orally, IV, SQ, epidurally
- May produce psychosis
- Long-term use can cause proximal muscle wasting – 4-6 weeks

Anticonvulsants

- Older agents have significant adverse effects (carbamazepine – aplastic anemia; phenytoin – hepatotoxicity)
- Gabapentin generally well tolerated – dizziness, sedation, dose – 100 TID or q HS and titrate up to 3600 mg/day
- Pregabalin – 50 mg po TID, increase over days to 300 mg/day

Anticonvulsants

- Case report of topiramate (Topamax) 25 mg q day, titrated upward to 50 mg twice daily provided relief of pain for one month, patient able to stand
- Residual paresthesias

Anticonvulsants (cont'd)

- Gabitril (tiagabine)
- Keppra (levetiracetam)
- Lamictal (lamotrigine)
- Topamax (topiramate)
- Trileptal (oxcarbazepine)
- Zonegran (zonisamide)

Backonja MM. *Neurology* 2002;59(5 Suppl 2):S14-S17.

Tricyclic Antidepressants

- Most studied agent, amitriptyline, has most anticholinergic effects
- Alternate agents: nortriptyline, desipramine
- Usually sedating, administer at night
- Start low, titrate gradually every 2 or 3 days
- Prevent constipation

Hammack JE, et al. *Pain* 2002; 98:195-203

Atypical Antidepressants

- Case report of relief of severe oxaliplatin-induced peripheral neuropathy relieved with 37.5 mg venlafaxine (Effexor) twice daily
- Residual paresthesias

Durand J-P, et al. *Anti-Cancer Drugs* 2005;16:587-591

Atypical Antidepressant

- Duloxetine (Cymbalta)
- Approved diabetic neuropathy
- 20 mg q day titrate to 60 mg q day
- Initial hypotension
- Cannot crush/cut tablet

Local Anesthetic

- Topical
 - EMLA® Cream
 - Lidoderm® patch
- Intravenous
- Epidural/intrathecal

Mao J, Chen LL. *Pain* 2000; 87:7-17

Assessment for Functional Dependence

- Can you get up from and down to a toilet?
- Can you get up and down a curb, steps, etc.?
- Can you dress, groom, bathe yourself?
- Have you fallen or almost fallen?
- Do you now require help to do things you formerly did independently?

Non-Pharmacological Strategies

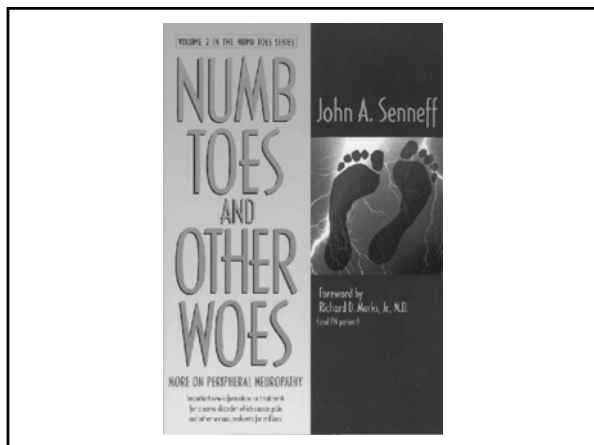
- Cognitive/behavior modification
 - Relaxation/guided imagery
 - Distraction
 - Cognitive reframing
 - Support groups
- Physical measures
 - Heat/cold/massage

Safety: Patient/Family Education

- Assess water temperature in the home
- Use protective gloves washing dishes
- Use pot holders
- Wear cotton socks
- Well-lit rooms without glare
- Clear walkways (no throw rugs)
- Non-skid showers and tub mats

Rehabilitation Interventions: Exercise

- To increase strength
 - of involved muscles
 - of accessory muscles
- To improve coordination
- To improve sensory integration
- To maintain muscle and ligamentous length and prevent deformity
- Progressive desensitization



Resources

- The Neuropathy Association
www.neuropathy.org
- Lance Armstrong Foundation
www.livestrong.org
- Conversations: The International Ovarian Cancer Connection
www.ovarian-news.org/neuropathy.html
- Neuropathy Trust
www.neuropathy-trust.org



Never doubt that a small group
of thoughtful, committed
citizens can change the world.
Indeed, it is the only thing that
ever has.

Margaret Mead
