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 – Thalidomide
  - Cisplatin – Vinblastine
  - Oxaliplatin – Vincristine
  - Paclitaxel

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

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

Unclear Terminology

Neuropathy (Paresthesia)  Pain

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


Assessment Not Standardized

<table>
<thead>
<tr>
<th>Tool</th>
<th>Validity</th>
<th>Language</th>
<th>Domains</th>
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<tbody>
<tr>
<td>NPS</td>
<td>DN, PhN, CRPS</td>
<td>36+</td>
<td>Burning, Sharp</td>
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<tr>
<td>FACT-Taxane</td>
<td>Extensive in cancer</td>
<td>45+</td>
<td>Numbness, ADL limitations</td>
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<tr>
<td>EORTC QLQ</td>
<td>Underway</td>
<td>English, French, Dutch</td>
<td>Tingling, numbness, pain, ADL limitations</td>
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<tr>
<td>CIPNS-32</td>
<td>Ovarian cancer</td>
<td>English</td>
<td>Paresthesias, numbness</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Tests</th>
<th>Findings</th>
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<tr>
<td>Chaudhry Ann Neurol, 1994</td>
<td>Neuro exam</td>
</tr>
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<td></td>
<td>Electrophysiology</td>
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<td>Forsyth J Neuro Onc, 1997</td>
<td>Thermal and vibration thresholds</td>
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<td>Dougherty Pain, 2004</td>
<td>Thermal, touch, sharp</td>
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<tr>
<td>Argyrious Support Care Cancer, 2005</td>
<td>Neuro exam</td>
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Grading Scales for Neuropathy

<table>
<thead>
<tr>
<th>Scale</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI-CTCAE</td>
<td>No symptoms, loss of DTR</td>
<td>Paresthesia, ADL ok</td>
<td>Paresthesia, ADL interference</td>
<td>Disabling</td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td>Mild Paresthesia, Loss DTR</td>
<td>Sensory loss, Paresthesia</td>
<td>Severe sensory and motor loss</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
<td>Weakness</td>
<td>with function</td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO</td>
<td>Paresthesia, Decreased DTR</td>
<td>Severe paresthesia</td>
<td>Intolerable</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
<td>Weakness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
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Postma TJ. 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)

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Patients Treated (Controls)</th>
<th>Controlled Trial</th>
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<tr>
<td>Penz et al 2001</td>
<td>Amifostine</td>
<td>15</td>
<td>No</td>
</tr>
<tr>
<td>Eckel et al 2002</td>
<td>Carbamazepine</td>
<td>10 (30)</td>
<td>No</td>
</tr>
<tr>
<td>Gedicka et al 2002</td>
<td>α-Lipoic acid</td>
<td>15</td>
<td>No</td>
</tr>
<tr>
<td>Cascini et al 2002</td>
<td>Glutathione +</td>
<td>26 (26)</td>
<td>Yes*</td>
</tr>
<tr>
<td>Durand et al 2003</td>
<td>Ventaflaxine</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>Marshall et al 2004</td>
<td>Gingko biloba</td>
<td>17</td>
<td>No</td>
</tr>
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Grothey A. Clin Colorectal Cancer 2005; Suppl 1:S38-S46

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<tr>
<td>Mariani et al 2000</td>
<td>Gabapentin</td>
<td>15</td>
<td>No</td>
</tr>
<tr>
<td>Mitchell et al 2006</td>
<td>Gabapentin</td>
<td>41</td>
<td>No</td>
</tr>
<tr>
<td>Garneline et al 2004</td>
<td>Ca$_2^+$ + Mg$_2^+$ Infusion +</td>
<td>96 (65)</td>
<td>Yes*</td>
</tr>
<tr>
<td>Argyriou et al 2005</td>
<td>Vitamin E +</td>
<td>16 (15)</td>
<td>Yes*</td>
</tr>
<tr>
<td>Cassidy et al 2006</td>
<td>Xaliproden +</td>
<td>324 (325)</td>
<td>Yes</td>
</tr>
</tbody>
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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


**CONcePT: Combined Oxaliplatin Neurotoxicity Prevention Trial**

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

Primary Endpoint: time to treatment failure

2 x 2 randomization

<table>
<thead>
<tr>
<th>RANDOMIZE</th>
</tr>
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</table>
| mFOLFOX7 plus Bevacizumab
  Continuous until treatment failure
| With or without intravenous Calcium/Magnesium
| mFOLFOX7 plus Bevacizumab
  Stop-and-go (Oxaliplatin)

Activation: January 2005

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 \( \mu \), Delta \( \delta \), Kappa \( \kappa \)
- Effective for neuropathic pain

Opioids
- Codeine
- Fentanyl
- Hydrocodone
- Hydromorphone
- Methadone
- Morphine
- Oxycodone
- Oxymorphone

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


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

Atypical Antidepressants

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


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*