Treatment of Chemotherapy Induced Peripheral Neuropathy

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Pharmacy Grand Rounds
January 26th, 2016
Objectives

- Describe the pathophysiology of chemotherapy induced peripheral neuropathy (CIPN)
- List common agents known to cause CIPN
- Review current recommendations for treatment of CIPN
- Compare the evidence of anticonvulsants vs antidepressants for CIPN
Neuropathic Pain (NP) and CIPN

- NP affects 3.8 million in the United States
  - Postherpetic neuralgia and painful diabetic neuropathy most common
- CIPN: overall incidence is ~38% in patients treated with multiple chemotherapy agents
  - Estimates as high as 90% of all cancer patients

## CIPN Presentation and Symptoms

<table>
<thead>
<tr>
<th>CIPN Types</th>
<th>Symptoms</th>
<th>Associated Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory</td>
<td>Numbness, loss of proprioception, tingling, “pins and needles”, stocking-glove distribution of hyperalgesia/allodynia</td>
<td>Most common type: platinum agents, vinca alkaloids, bortezomib, taxanes</td>
</tr>
<tr>
<td>Motor</td>
<td>Muscle weakness, cranial nerve deficits, paclitaxel-associated acute pain syndrome (P-APS)</td>
<td>Paclitaxel, vincristine</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Orthostatic hypotension, constipation, and erectile dysfunction</td>
<td>Vinca Alkaloids</td>
</tr>
</tbody>
</table>

Brewer et al. *Gynecol Oncol* 2015; 140:176-83
Pathophysiology of CIPN

α2δ1 subunit upregulation
**Pathophysiology of CIPN Summary**

<table>
<thead>
<tr>
<th>Taxanes (paclitaxel, docetaxel)</th>
<th>Vinca Alkaloids (vincristine, vinblastine, vinorelbine)</th>
<th>Platin (oxaliplatin, cisplatin, carboplatin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• *Neuronal injury and inflammation</td>
<td>• Disrupt axonal transport</td>
<td>• *Neuronal damage from ion channel dysregulation (especially Na⁺)</td>
</tr>
<tr>
<td>• Disrupt axonal transport</td>
<td>• Oxidative stress and inflammation</td>
<td>• Oxidative stress and inflammation</td>
</tr>
<tr>
<td>• ↑ ion channel activity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mPTP = mitochondrial permeability transition protein
CIPN Risk Factors – Patient Specific

- Prior/current treatment with a neurotoxic agent
- Increasing age
- Diabetes mellitus - independent risk factor
- Preexisting conditions that cause nerve damage
  - Alcohol use, folate/vitamin B12 deficiency

Brewer et al. *Gynecol Oncol* 2015; 140:176-83
CIPN Risk Factors – Agent Specific

- Chemotherapy agent
  - Concomitant use of other chemotherapeutic agents
  - E.g. carboplatin plus paclitaxel for ovarian malignancies
- Duration of therapy
- Cumulative dose

Brewer et al. Gynecol Oncol 2015; 140:176-83

P-APS= paclitaxel associated pain syndrome
Impact of CIPN

• Pain can resolve in weeks or persist for years
  • 15% of breast cancer survivors treated with docetaxel report CIPN 1-3 years after treatment
  • 15% of 120 ovarian cancer patients treated carboplatin + paclitaxel had CIPN after 6 months
    • 11% with CIPN after 2 years

• Influence treatment decisions
  • Receive less chemotherapy or cycles
  • Selection different agents

• Decrease in health-related quality of life (HRQOL)

Eckhoff et al. Eur J Cancer 2015; 51:292-300
Brewer et al. Gynecol Oncol 2015; 140:176-83.
Patient Case

• 45 year old female with colorectal carcinoma s/p neoadjuvant FOLFOX + bevacizumab
  • Fluorouracil, leucovorin, oxaliplatin

• Presents POD 1 after resection of her disease

• She complains of 4/10 pain described as “pins and needles” feeling in both hands and feet

• History of hypertension and current medications include:
  • Morphine ER 30 mg BID
  • Amlodipine 10 mg daily
Case Question #1

• Which of the following agents most likely caused her neuropathy?
  A. Fluorouracil
  B. Leucovorin
  C. Oxaliplatin
  D. Bevacizumab
Case Question #2

• Which of the following describes the pathophysiology of oxaliplatin CIPN?
  A. Disrupts axonal transport via tubulin depolarization inhibition
  B. Oxidative stress and inflammation
  C. Ca$^{2+}$ chelation by oxalate
  D. Both B and C
CIPN – Treatment Overview

- **Goals of therapy**
  - Relieve symptoms
  - Minimize adverse effects

- **Non-pharmacologic therapy**
  - Physical therapy
  - Psychological coping techniques

- **Pharmacologic therapy**
  - Start with low doses, titrate slow
  - Monitor for adverse effects

## Current Guideline Recommendations

<table>
<thead>
<tr>
<th>ASCO Guidelines 2014</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Line</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Limited efficacy or not enough evidence</td>
<td>Gabapentin, pregabalin, amitriptyline, nortriptyline, topical gel with amitriptyline, baclofen and ketamine</td>
</tr>
<tr>
<td>Not recommended</td>
<td>Acetyl-l-carnitine, lamotrigine</td>
</tr>
</tbody>
</table>

ASCO: American Society of Clinical Oncology

Antidepressants for CIPN

- SNRI and TCA
  - Duloxetine and venlafaxine
  - Amitriptyline and nortriptyline
- Serotonin and norepinephrine suppress transmission of pain stimuli
  - Inhibits afferent neuron conduction into dorsal horn
- TCA also blocks α-adrenergic receptors blockade
  - Muscarinic and histaminergic blockade

SNRI = Serotonin and norepinephrine reuptake inhibitors
TCA = Tricyclic antidepressants

Brewer et al. *Gynecol Oncol* 2015; 140:176-83
### Venlafaxine and TCAs for CIPN

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Intervention (chemotherapy)</th>
<th>Primary endpoint</th>
<th>Findings (p-value)</th>
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</thead>
<tbody>
<tr>
<td>Hammack et al. (n=51)</td>
<td>Nortriptyline (25 mg, titrate to 100 mg daily) vs placebo over 4 weeks with cross over (cisplatin)</td>
<td>Relief in paresthesia in first treatment period</td>
<td>No significant difference (p=0.78)</td>
</tr>
<tr>
<td>Kautio et al. (n=44)</td>
<td>Amitriptyline (10 mg, titrate to 50 mg daily) vs placebo over 8 weeks (vinca alkaloids, platinum, taxanes)</td>
<td>Relief of neuropathic pain assessed by diary</td>
<td>Mean global improvement amitriptyline = 3.4, PL=1.9 (p = not significant)</td>
</tr>
<tr>
<td>Durand et al. (n=48)</td>
<td>Venlafaxine (50 mg day 1, 37.5 mg BID days 2-11) vs placebo during cycles of chemotherapy (oxaliplatin)</td>
<td>Percentage of patients with 100% pain relief</td>
<td>Venlafaxine 31.3%, placebo 5.3% (p=0.03)</td>
</tr>
</tbody>
</table>

Duloxetine for CIPN

• Randomized, double blinded, placebo controlled cross over trial
• Placebo vs duloxetine 30 mg x 1 week, 60 mg x 4 weeks
• Primary endpoint: mean change in average pain severity
  • Utilized the BPI-SF items
  • 11 point scale

Duloxetine for CIPN - Study Flow Chart

Study Group n=231
+ Platin or taxane
+ >3 month duration of CIPN post chemotherapy
+ ≥ Grade 1 sensory pain
+ 4/10 reported average pain
- History of neuropathy from other etiology

Adjuvant medications:
Stable dose 2 weeks prior
No dose changes during trial

Group A
Duloxetine n=115

Group B
Duloxetine n=93

Group B
Placebo n=116

Group A
Placebo n=85

Duloxetine for CIPN - Results

Group A: Duloxetine first, Placebo second
Group B: Placebo first, Duloxetine second

Duloxetine for CIPN – Results

• Numerical trend toward greater benefit in platins than taxanes
  • Mean difference of 1.06 vs 0.19 respectively
  • \( p = 0.13 \)

• Pain interference with daily function and QOL improved in duloxetine vs placebo

Antidepressants for CIPN – Conclusions

• Duloxetine 60 mg daily effective in CIPN
  • Future studies look at specific chemotherapies

• Insufficient evidence for TCAs in CIPN

• Insufficient evidence for venlafaxine in CIPN
  • Very small trial
  • Trial looking at higher doses
    • 75 mg/day -> acts like SSRI
    • 225-375 mg/day -> acts like SNRI
Anticonvulsants for CIPN

• Gabapentin and pregabalin
• Bind to $\alpha_2\delta1$ subunit of presynaptic Ca$^{2+}$ channels
  • Inhibit release of excitatory neurotransmitters
  • Upregulated after nerve injury in DRG in animal studies
    • Specifically mechanical and diabetic neuropathy
    • Not up-regulated in CIPN
• Lamotrigine binds to Na$^+$ and Ca$^{2+}$ channels
Gabapentin for Neuropathic Cancer Pain

• 121 patients with cancer induced NP over 10 days
  • Infiltration or compression into nerve structures
  • Stable dose of regularly scheduled opioids

• Excluded patients receiving chemotherapy

• Significant difference between average pain scores at day 10
  • Gabapentin 4.6 vs placebo 5.4 (p=0.0250)
  • Adverse events in 43.7% gabapentin patients

Gabapentin for CIPN

- 6 week randomized, double-blind, crossover trial
  - Titrated up over 3 weeks to target dose of 900 mg TID
    - Regardless of efficacy at lower doses
- Primary endpoint was improvement in average pain in NRS and ENS

ENS: Eastern Cooperative Oncology Group neuropathy scale
NRS: Numeric Rating Scale

Gabapentin for CIPN - Study Flow Chart

Study Group n=115
+ ≥ 1 ENS
+ ≥ 4/10 NRS Pain
- History of neuropathy from other causes
- Baseline pain adjuvant medications (could be started after study initiation)

Group 1
Gabapentin
n=57

Group 2
Placebo
n=58

Group 2
Gabapentin

6 weeks

Group 1
Gabapentin

2 weeks

Group 1
Placebo

6 weeks

ENS: Eastern Cooperative Oncology Group neuropathy scale
NRS: Numeric rating scale


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Gabapentin for CIPN – Average Pain Scores

*No statistically significant differences between groups

G/P = Gabapentin first 6 weeks, Placebo weeks 8-14
P/G = Placebo first 6 weeks, Gabapentin weeks 8-14
ENS: Eastern Cooperative Oncology Group neuropathy scale
NRS: Numeric Rating Scale

### Lamotrigine and Pregabalin for CIPN

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<td>Lamotrigine up to 150 mg BID vs placebo over 10 weeks (vinca alkaloids, platinum, taxanes)</td>
<td>Mean decrease in average pain score</td>
<td>Lamotrigine 0.3, Placebo 0.5 (p=0.56)</td>
</tr>
</tbody>
</table>

- No randomized control in CIPN published for pregabalin
- 1 pregabalin trial for CIPN in colorectal cancer terminated
- Systemic literature review of pregabalin for neuropathic cancer pain inconclusive

Information from clinicaltrials.gov accessed 1/20/2016
Anticonvulsants for CIPN - Summary

- Gabapentin can be used for cancer-related neuropathy
  - Insufficient evidence for CIPN
- Negative evidence for lamotrigine
- Insufficient evidence for pregabalin in CIPN
## Topical Agents

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>Intervention (chemotherapy)</th>
<th>Primary Endpoint</th>
<th>Findings (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barton et al. 2011 (n=44)</td>
<td>Baclofen 10 mg, amitriptyline 40 mg, ketamine 20 mg gel (BAK) vs placebo applied BID over 4 weeks (vinca alkaloids, platinum, taxanes, thalidomide)</td>
<td>Mean baseline-adjusted difference in sensory subscale of the EORTC QLQ-CIPN20</td>
<td>BAK = 8.1, Placebo= 3.8 (p = 0.053)</td>
</tr>
<tr>
<td>Gewandter et al. 2013 (n=48)</td>
<td>Amitriptyline 4% and ketamine 2% (AK) cream applied BID vs placebo over 6 weeks (taxanes, non-taxanes)</td>
<td>Average pain score (NRS out of 10) at 6 weeks</td>
<td>AK 4.93, placebo 5.19 (p=0.132)</td>
</tr>
</tbody>
</table>

Case question #3

Which of the following agents would you recommend initiating for our patient? (amlodipine and morphine home medications)

A. Gabapentin
B. Duloxetine
C. Topical amitriptyline and ketamine
D. Venlafaxine

B. Duloxetine
Question #4

Which of the following is true regarding anticonvulsants and antidepressants in treating NP in cancer patients?

A. The combination of baclofen, amitriptyline and ketamine improves sensory pain and was demonstrated in its trial

B. Gabapentin was shown to be effective for cancer related neuropathy, but not CIPN

C. Duloxetine improves pain more in taxane related CIPN than platin related CIPN

D. Venlafaxine has been shown to be effective in paclitaxel CIPN
Conclusion

- **Duloxetine**
  - **Gabapentin** (if neuropathic cancer pain)

- **Venlafaxine**
  - **Pregabalin**
  - **TCA**
  - **Topical gels**
Treatment of Chemotherapy Induced Peripheral Neuropathy

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Adverse Effects Associated With Duloxetine

<table>
<thead>
<tr>
<th>Adverse event, No. (%)</th>
<th>Group A (n = 96)</th>
<th>Group B (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pain</td>
<td>4 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (4)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

There were no grade 4 or 5 adverse events. Only adverse events occurring in ≥ 3% are reported above.
PN – Pharmacologic agents

Perception
Cognitive behavioral approaches

Descending inhibition
TCAs: e.g. nortriptyline
SNRIs: e.g. duloxetine
Opioids: e.g. morphine

Spinal transmission
GABAr: e.g. gabapentin
NMDAr: e.g. ketamine
Opioids: e.g. morphine

Peripheral transduction
VGSC: e.g. lidocaine, carbamazepine
TRPV1: e.g. capsaicine

Cerebral cortex

Image from
Duloxetine for CIPN – Results

- Multivariate logistic regression in first 5 weeks
- Adjusted for chemo agent, high risk of developing CIPN and baseline pain score

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comparison</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% decrease</td>
<td>Duloxetine : Placebo</td>
<td>2.79</td>
<td>1.14, 6.90</td>
<td>0.025</td>
</tr>
<tr>
<td>30% decrease</td>
<td>Duloxetine : Placebo</td>
<td>2.29</td>
<td>1.12, 4.69</td>
<td>0.023</td>
</tr>
</tbody>
</table>

- Pain interference with daily function and QOL improved in duloxetine vs placebo
  - p=0.01 and p = 0.03 respectively
Prevention of CIPN

- Reduce dose or duration of chemotherapy
- No agent has shown enough benefit to be considered for prevention of CIPN

None currently recommended by ASCO guidelines

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetyl-L-carnitine</td>
</tr>
<tr>
<td>Amifostine</td>
</tr>
<tr>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Ca / Mg infusion</td>
</tr>
<tr>
<td>Gabapentin</td>
</tr>
<tr>
<td>Glutathione</td>
</tr>
<tr>
<td>Nimodipine</td>
</tr>
<tr>
<td>Org 2766</td>
</tr>
<tr>
<td>Retinoic Acid</td>
</tr>
<tr>
<td>Omega fatty acids</td>
</tr>
<tr>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Vitamin E</td>
</tr>
<tr>
<td>Glutamate</td>
</tr>
<tr>
<td>Oxycarbazepine</td>
</tr>
<tr>
<td>Venlafaxine</td>
</tr>
</tbody>
</table>

ASCO : American Society of Clinical Oncology

Brewer et al. Gynecol Oncol 2015; 140:176-83.
## Gabapentin for CIPN

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>P-value</th>
<th>End of 6 weeks</th>
<th>P-value</th>
<th>End of 14 weeks</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = G/P</td>
<td>57</td>
<td>-</td>
<td>38</td>
<td>-</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>N = P/G</td>
<td>58</td>
<td>-</td>
<td>39</td>
<td>-</td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td>ENS* G/P</td>
<td>1.9</td>
<td>0.7</td>
<td>1.7</td>
<td>0.3</td>
<td>1.5</td>
<td>0.7</td>
</tr>
<tr>
<td>ENS* P/G</td>
<td>2.0</td>
<td>1.8</td>
<td>0.3</td>
<td>1.5</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>NRS* G/P</td>
<td>4.3</td>
<td>0.06</td>
<td>3.3</td>
<td>0.8</td>
<td>3.1</td>
<td>0.2</td>
</tr>
<tr>
<td>NRS* P/G</td>
<td>3.6</td>
<td></td>
<td>3.0</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*=Average Pain

G/P=Gabapentin first 6 weeks, Placebo weeks 8-14
P/G=Placebo first 6 weeks, Gabapentin weeks 8-14
ENS: Eastern Cooperative Oncology Group neuropathy scale
NRS: Numeric Rating Scale

## Duloxetine for CPIN – Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n=109)</th>
<th>Group B (n=111)</th>
<th>Total (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>60 (10.4)</td>
<td>59 (10.6)</td>
<td>59 (10.5)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>71 (65)</td>
<td>67 (60)</td>
<td>138 (63)</td>
</tr>
<tr>
<td>Paclitaxel (%)</td>
<td>44 (40)</td>
<td>43 (39)</td>
<td>87 (40)</td>
</tr>
<tr>
<td>Oxaliplatin (%)</td>
<td>63 (58)</td>
<td>66 (59)</td>
<td>129 (59)</td>
</tr>
<tr>
<td>Breast Cancer (%)</td>
<td>41 (38)</td>
<td>42 (38)</td>
<td>83 (38)</td>
</tr>
<tr>
<td>GI Cancer (%)</td>
<td>63 (58)</td>
<td>66 (59)</td>
<td>129 (59)</td>
</tr>
<tr>
<td>Mean Pain Score at Baseline* (SD)</td>
<td>6.1 (1.7)</td>
<td>5.6 (1.6)</td>
<td>5.8 (1.7)</td>
</tr>
</tbody>
</table>

*statistically significant difference $p=0.02$

Group A: Duloxetine first, Placebo second  
Group B: Placebo first, Duloxetine second  

## Lamotrigine and Pregabalin for CIPN

<table>
<thead>
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<th>Study (n)</th>
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<td>Mean decrease in average pain score</td>
<td>Lamotrigine 0.3, Placebo 0.5 (p=0.56)</td>
</tr>
<tr>
<td>Saif et al. (n=23)</td>
<td>Pregabalin up to 150 mg TID (Oxaliplatin)</td>
<td>Decrease of one grade severity in neuropathic pain</td>
<td>70% response, 150 mg TID 22%, 100 mg TID 35%</td>
</tr>
</tbody>
</table>