NCI Symptom Management and Quality of Life Steering Committee Clinical Trials Planning Meeting on Chemotherapy Induced Peripheral Neuropathy

Charles Loprinzi, MD
cloprinzi@mayo.edu
Topics

• Introductory comments
• A picture of the problem
• Prevention of CIPN-story for a sample study
• Summary statements
• Discussion
Chemotherapy-Induced Peripheral Neuropathy

• Major oncologic problem

• Common chemotherapy dose limiting toxicity

• Affects life quality

• Promising preliminary results regarding effective prevention and treatment of this problem
Meeting Data

- March 23, 2009
- Approximately 100 participants
- Thought-provoking presentations/discussion
- Report provided
- Informal reviews/remarks
Topics

• Introductory comments
• A picture of the problem
• Prevention of CIPN-rationale for 2 sample studies
• Summary statements
• Discussion
Abnormal Innervation following Chemotherapy

Epidermal Nerve Fibers (ENFs)

Normal palm: 20x magnification

Site A: No ENFs

20x magnification
Meissner’s Corpuscles from finger tip

Normal Meissner’s Corpuscles

Abnormal Meissner’s Corpuscles

Measurement issues

• Multiple proposed tools

• Work is needed to fine tune means to delineate the fine aspects of CIPN

• Different symptoms

• Differences between drugs
Topics

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Intravenous Calcium and Magnesium for Oxaliplatin-Induced Sensory Neurotoxicity (N04C7)

DA Nikcevich, A Grothey, JA Sloan, JW Kugler, PT Silberstein, T Dentchev, DB Wender, PJ Novotny, HE Windschitl, CL Loprinzi

For the North Central Cancer Treatment Group

J Clin Oncol 2008; May 20 suppl (abstract 4009)
It was proposed that CaMg would stabilize nerve membranes and prevent the accumulation of oxaliplatin in DRG.

In a retrospective, non-randomized study, intravenous administration of calcium and magnesium salts (CaMg) was associated with reduced oxaliplatin-induced PSN (Gamelin: Clin Cancer Res, 2004).
N04C7 Cancer Control Phase III Trial – Study Design

Patients to receive adj FOLFOX

R

IV CaMg  IV placebo

% of grade 2+ sNT
N04C7 Cancer Control Phase III Trial

– Study Stopped Early

– 102 pts/300 planned
Primary Endpoint Grade 2+ sNT (CTCAE Scale)

<table>
<thead>
<tr>
<th>Neurotoxicity grade</th>
<th>CaMg n=50</th>
<th>Placebo n=52</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2+</td>
<td>22%</td>
<td>41%</td>
<td>0.038</td>
</tr>
</tbody>
</table>
Time to Grade 2+ sNT (CTC scale)

% Free

Ca/Mg

Placebo

P=0.05

Weeks
Concept Trial Story

• Stop and go oxaliplatin question
• CaMg vs not question
• Slower accrual than desired
• Stop CaMg vs placebo part….all to get CaMg
• Data management committee…. 

FOLFOX $\rightarrow$ R$^*$

- CaMg – 2 doses
- CaMg – 1 dose
- Placebo – 2 doses
Other Promising Appearing Agents

• Glutathione
• Alpha lipoic acid/thiotic acid
• Acetyl-L-carnitine
• Duloxetine/Cymbalta
• Baclofen/amitriptyline/ketamine
Topics

- Introductory comments
- A picture of the problem
- Prevention of CIPN-story for a sample study
- Summary statements
- Discussion
Summary statements

• CIPN is a major clinical problem

• Chemotherapy can cause structural nerve damage

• There is sufficient rationale for conducting high quality clinical trials
Summary statements

• Efforts are needed to
  • better understand genetic variations that will predict for CIPN
  • better define CIPN targets and mechanism based therapies to prevent and/or treat CIPN

• There is a need for more animal model experiments to help direct clinical trial options
Summary statements

• I, even as a conservative investigator, firmly believe that positive clinical trials, with clinically significant results, will be forthcoming within the next few years.

• More mechanism based research will improve efforts to define effective therapies.
Topics

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Thank you
Prevention of CIPN

• Acetyl L-Carnitine (ALC)
Neuropathy results from disruption of mitochondrial DNA synthesis in nerve cells. Mitochondrial metabolism in the neurons is decreased and the cells’ long peripheral axons die back, causing pain, tingling, and numbness.
Prevention of paclitaxel-evoked painful peripheral neuropathy by acetyl-L-carnitine

Withdrawal responses from hind paws Normal rats rarely withdraw from the 4 g stimulus; increased responding after paclitaxel treatment is indicative of mechano-allodynia.
Axonal Mitochondria

- Atypical and normal mitochondria in C-fibers (A) and A-fibers (B).

- Swollen and vacuolated mitochondria shown at arrows; barred arrows point to normal mitochondria.

- A mixture of normal and swollen and vacuolated mitochondria were often found within the same axon.

- These examples are from a paclitaxel-treated rat that received ALCAR injections.
S0715: Randomized Placebo-Controlled Trial Of Acetyl L-Carnitine For The Prevention Of Taxane Induced Neuropathy

History of stage I, II, or IIIA, About to initiate taxane-based chemotherapy

- Paclitaxel at 175 mg/m2 QOWx 4
- Paclitaxel at 80 mg/m2 x 12 w
- TAC (docetaxel 75 mg/m2) q3weeks x 6
- TC

(N = 190/arm)

Follow-up: 12 weeks, 24 weeks, 36 weeks, 1 year

Main Outcome: Change in Neurotaxane subscale of the FACT-TAX
Secondary: CTC; Fatigue; NGF; Dose/Compliance
Bayer: Phase II Randomized Placebo-Controlled Trial Of Acetyl L-Carnitine For The Prevention Of Sagopilone Induced Neuropathy

Prostate or Ovarian Cancer
Grade 0 CTC PN
About to initiate Sagopilone on efficacy trial

Randomize

ALC
1 gm TID x 24 weeks

Placebo
1 gm TID x 24 weeks

Follow-up: 6 cycles
Main Outcome: CTCAE PN Grade
Secondary Outcomes- treatment discontinuation; incidence of grade 3/4
Prevention of CIPN

• Alpha-Lipoic Acid / Thiotic Acid
Alpha-Lipoic Acid / Thiotic Acid

- A potent lipophilic antioxidant
- Oxidative stress implicated in pathogenesis of diabetic PN
- 7 RCTs trials of thioctic acid in diabetic PN completed
- Meta-analysis conclusions
  - Short-term treatment using IV thioctic acid 600 mg/day reduces symptoms of diabetic PN
  - Improvement of neuropathic deficits
  - Oral treatment for 4-7 m. reduces neuropathic deficits
  - Improve cardiac autonomic neuropathy
  - Studies revealed a favorable safety profile
MDACC: Prevention of Cisplatin or Oxaliplatin-induced PN with Alpha Lipoic Acid: A Placebo-Controlled Phase III Trial

Scheduled to receive platinum
No clinical neuropathy
No neurotoxic chemo for 6 mos prior
Stratified prior platinum therapy

(RANDOMIZE)

Alpha Lipoic Acid TID x 24 weeks
Placebo TID x 24 weeks

(N = 244 pts)

Follow-up: 6-8; 12; 24; 36; 48
Main Outcome: Severity and frequency of PN; FACT-GOG-NTX
Secondary: functional tests, chemotherapy courses/doses,
Prevention of CIPN-Glutathione
Glutathione

- Tripeptide consisting of 3 amino acids: glutamyl-cysteinyl-glycine
- Naturally occurring compound
- Felt to be nontoxic
- High affinity for heavy metals
Glutathione
Glutathione → Glutathione S transferase → Sulfur substituted glutathione
Glutathione

• Initially thought to be able to prevent cisplatin-induced nephrotoxicity

• In animal studies utilizing cisplatin, GSH did decrease nephrotoxicity and neurotoxicity
Glutathione

- Some evidence that GSH decreases cisplatin-induced nephrotoxicity in humans
- Some preliminary clinical trials, designed to look at nephrotoxicity, revealed a lower than expected incidence of neurotoxicity
Platinum neurotoxicity

From accumulation of platinum in dorsal room ganglia
Glutathione

- Decreases the accumulation of platinum in dorsal root ganglia
- Regulates calcium channel kinetics
- This might be responsible for how it helps to prevent neurotoxicity
- It may also affect other ion channel pathways
Randomized Glutathione Trials
# Glutathione for Advanced Gastric Cancer/CDDP

<table>
<thead>
<tr>
<th></th>
<th>GSH n=25</th>
<th>Placebo n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>20%</td>
<td>12%</td>
</tr>
<tr>
<td>Partial response</td>
<td>56%</td>
<td>40%</td>
</tr>
<tr>
<td>Overall response</td>
<td>76%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>Median overall survival</strong></td>
<td>14 mo</td>
<td>10 mo</td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 9</td>
<td>0%</td>
<td>66%</td>
</tr>
<tr>
<td>Week 15</td>
<td>17%</td>
<td>88%</td>
</tr>
</tbody>
</table>
Glutathione for Oxaliplatin/Advanced Colorectal Cancer (1)

<table>
<thead>
<tr>
<th>Therapy administered</th>
<th>Glutathione n=26</th>
<th>Placebo n=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cycles</td>
<td>175 (median – 8)</td>
<td>172</td>
</tr>
<tr>
<td>Dose intensity</td>
<td>39.2 mg/m²/wk</td>
<td>38.8 mg/m²/wk</td>
</tr>
<tr>
<td>Median total dose</td>
<td>782 mg</td>
<td>783 mg</td>
</tr>
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</table>

## Glutathione for Oxaliplatin/Advanced Colorectal Cancer (2)

<table>
<thead>
<tr>
<th></th>
<th>Glutathione n=26</th>
<th>Placebo n=26</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antitumor activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>27%</td>
<td>23%</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>7 mo</td>
<td>7 mo</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>16 mo</td>
<td>17 mo</td>
</tr>
</tbody>
</table>

Cascinu et al
### Glutathione for Oxaliplatin/Advanced Colorectal Cancer (3)

<table>
<thead>
<tr>
<th></th>
<th>Glutathione n=26</th>
<th>Placebo n=26</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropathy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>After 4 cycles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I-II</td>
<td>27%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td><strong>After 8 cycles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>43%</td>
<td>79%</td>
<td>0.04</td>
</tr>
<tr>
<td>Grade II-IV</td>
<td>10%</td>
<td>58%</td>
<td>0.003</td>
</tr>
<tr>
<td>Grade III-IV</td>
<td>0%</td>
<td>26%</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>12 cycles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II-IV</td>
<td>30%</td>
<td>100%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Cascinu et al
### Glutathione for Advanced Ovarian Cancer/CDDP (1)

<table>
<thead>
<tr>
<th></th>
<th>Glutathione n=74</th>
<th>Placebo n=77</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received 6 cycles</td>
<td>58%</td>
<td>39%</td>
<td>0.04</td>
</tr>
<tr>
<td>Received 6 cycles at 100 mg/m²</td>
<td>23%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Mean no. of full dose courses</td>
<td>3.61</td>
<td>3.14</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean total no. of course received</td>
<td>4.80</td>
<td>4.38</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean total dose</td>
<td>440 mg/m²</td>
<td>441 mg/m²</td>
<td>0.13</td>
</tr>
</tbody>
</table>

# Glutathione for Advanced Ovarian Cancer/CDDP (2)

<table>
<thead>
<tr>
<th></th>
<th>Glutathione n=74</th>
<th>Placebo n=77</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response rate</td>
<td>73%</td>
<td>62%</td>
<td>0.25</td>
</tr>
<tr>
<td>Complete response via second look laparotomy</td>
<td>6/13 pt</td>
<td>1/11 pt</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean weight gain</td>
<td>2 kg</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>39%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Neurosensory toxicity</td>
<td>39%</td>
<td>49%</td>
<td>0.22</td>
</tr>
</tbody>
</table>

## Glutathione for Relapsed Ovarian Cancer/CDDP (n=33)

<table>
<thead>
<tr>
<th>Therapy delivered</th>
<th>Glutathione n=33/2</th>
<th>Placebo n=33/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 85% dose intensity</td>
<td>94%</td>
<td>60%</td>
</tr>
<tr>
<td>Antitumor activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response rate</td>
<td>75%</td>
<td>60%</td>
</tr>
<tr>
<td>Complete response</td>
<td>44%</td>
<td>27%</td>
</tr>
<tr>
<td>Median survival</td>
<td>21 mo</td>
<td>15.9 mo</td>
</tr>
<tr>
<td>Mean sural nerve sensory amplitude potential after 9 wk, compared to baseline values</td>
<td>-26%</td>
<td>-43%</td>
</tr>
</tbody>
</table>

Glutathione for Ovarian Cancer/CDDP

Overall response rate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione</td>
<td>16</td>
<td>75%</td>
</tr>
<tr>
<td>No treatment</td>
<td>17</td>
<td>60%</td>
</tr>
</tbody>
</table>

Glutathione Neuropathy Prevention, N08CA

- Ovarian type CA
- CBDCA/Taxol
- First cycle

GSH
Placebo