Adjuvant Vitamin E and Ovarian Cancer

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Introduction
• Ovarian Cancer
• Cisplatin
• Vitamin E

Question

Hypothesis

Experimental Design

Results

Summary

Future Studies
Ovarian Cancer

- 5th leading cause of cancer-related deaths in women in the U.S.
  - Accounts for about 6% of deaths
- Highest mortality rate of gynecologic cancers
- Most patients have widespread disease at diagnosis
Cisplatin (CDDP)

- Platinum containing chemotherapeutic drug
- Highly active against a number of cancers:
  - Ovarian, Lung, Cervical, Head & Neck, Testicular
- Side effects include:
  - Nephrotoxicity, ototoxicity, and **neurotoxicity**
CDDP-Induced Neuropathy (CIPN)

- Affects the nerves that carry sensations to the brain
- Major dose-limiting adverse side effect of CDDP
- Symptoms include:
  - Tingling & burning in hands and feet
  - Tremors
  - Numbness
CDDP-induced Neuropathy & Vitamin E

- Mechanism of CIPN is undetermined.
  - Platinum accumulation

- Clinical and histologic features are similar to those seen in Vitamin E deficiency neuropathy. (Muller ‘83, Sokol ’88)

- CDDP decreases plasma Vitamin E in humans. (Weigl ’98)
Vitamin E (RRR-α-Tocopherol)

- **RRR-α-Tocopherol (α-T):** natural form of vitamin E preferentially retained in the body. (Traber ’05)
Antioxidant role of α-T

- Lipid soluble antioxidant
  - Found in cell membranes

- Protects cellular lipids from oxidation
  - lipid peroxidation

- Biomarkers of Lipid peroxidation:
  - $F_2$-Isoprostanes
  - Malondialdehyde (MDA)
Central Question

Can the neurotoxicity of CDDP be mitigated to allow increased survival without decreased quality of life for ovarian cancer patients?
Central Hypothesis:

1) CDDP depletes tissue α-T by an oxidative stress mechanism leading to neurotoxicity

2) Adjunct α-T will prevent CDDP-mediated α-T depletion, thereby preventing neurologic damage

3) Adjuvant α-T will not decrease CDDP anti-tumor efficacy
**Pre-clinical Model of Ovarian Cancer**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Saline IP inject cells</td>
</tr>
<tr>
<td>B</td>
<td>α-T IP inject cells</td>
</tr>
<tr>
<td>C</td>
<td>Cisplatin IP inject cells</td>
</tr>
<tr>
<td>D</td>
<td>α-T/Cisplatin IP inject cells</td>
</tr>
</tbody>
</table>

* Rats treated with CDDP receive an accumulative dose of 18mg / kg
Adjuvant α-T does not alter CDDP-induced weight loss
Adjuvant $\alpha$-T increases CDDP Anti-tumor Efficacy
Adjuvant α-T decreases Tumor Incidence and Multiplicity

<table>
<thead>
<tr>
<th>Tumors Per Rat</th>
<th>0</th>
<th>&lt;10</th>
<th>10-50</th>
<th>50-100</th>
<th>100+</th>
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<tbody>
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<td></td>
<td></td>
<td>2/8</td>
<td>6/8</td>
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<tr>
<td>Group B</td>
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<td>8/12</td>
<td></td>
<td>3/12</td>
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<tr>
<td>Group C</td>
<td>2/16</td>
<td>2/16</td>
<td>1/16</td>
<td>8/16</td>
<td>3/16</td>
</tr>
<tr>
<td>Group D</td>
<td>10/16</td>
<td>2/16</td>
<td>2/16</td>
<td>1/16</td>
<td>1/16</td>
</tr>
</tbody>
</table>
Adjuvant α-T prevents tumor- and CDDP-induced depletion of α-T

* = p<0.05 vs. non-tumor controls; # = p<0.05 vs. saline treated tumor-bearing rats
Adjuvant α-T improves spinal cord α-T levels compared to CDDP alone

* = p<0.05 compared to non-tumor controls; # = p<0.05 compared to saline treated tumor-bearing rats.
Adjuvant α-T prevents tumor- and CDDP-induced elevation of plasma F₂-Isoprostanes

* = p<0.05 compared to non-tumor controls; # = p<0.05 compared to saline treated tumor-bearing rats.
Adjuvant α-T reduces spinal cord and lung platinum but not tumor platinum.

* = p<0.05 compared CDDP alone
Summary

α-T plus CDDP:

- Increases CDDP anti-tumor efficacy
  - Decreased tumor burden
- Prevents CDDP-induced decreases in tissue and plasma α-T
- Prevents tumor- and CDDP-induced lipid peroxidation
- Decreases accumulation of platinum in spinal cord tissues but not tumors
Ongoing & Future Studies

Ongoing Studies:

- Tissue analysis
  - MDA – oxidative stress
  - Glutathione – antioxidant
- Histology
  - Proliferation markers

Future Work:

- Adjuvant Vitamin C
- Clinical Trials
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Questions?
Pilot Study in Healthy Rats: CDDP Decreases Ganglia α-T **

** Columns within the same tissue but with different letter designations are significantly different, p<0.05
Lipid Peroxidation

1) Initiation
   • Production of a carbon radical

2) Propagation
   • Peroxyl radical and an additional carbon radical are formed

3) Termination
   • Two peroxyl radicals combine to stop the chain reaction
$F_2$-Isoprostane from Arachidonic Acid