Hemocyanins: Present and future relevance in superficial bladder carcinoma

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KLH and Olsson’s Serendipitous Discovery

- 1970’s: Cellular immune response is shown to be important in cancer
- KLH: used to determine cellular response by skin test reaction
- 1974: Olsson immunizes 10 BT patients with 5mg KLH to determine immunocompetence
- No correlation possible: only 3/10 have BT recurrence, compared with 7/10 before KLH
KLH and Olsson’s Serendipitous Discovery

• 1974: Olsson follows with a controlled trial
• 9 get 5mg KLH sc, 10 controls
• Follow: 204 and 228 pt months, respectively
• Recurrence 1/9 (11%) with KLH versus 7/10(70%) with control. A 59% reduction of tumor recurrence with a single, innocuous cutaneous immunization!

KLH and Olsson’s Serendipitous Discovery

- Olsson did not pursue his finding. Why? Moving from Boston (Boston U) to New York (Columbia U) he lost his data.
- We evaluated KLH in the animal model, publishing positive results in 1981, but believed BCG was more effective ...
- Klippel and Jurincic, hearing Olsson lecture in Germany, developed KLH from animal models to clinical trials*

KLH Immune Effects

- Studies in 9 animal species show strong cellular and humoral immune stimulation
- Doses ranging from 0.0025 to 250mg/kg
- Lymphoblastogenesis, T cells, KLH specific T helper cells, Macrophages, Basophils, IgA, IgG, IgM
- Toll immunity
- Thomsen Freidenreich Antigen
Anti-Tumor Effects of KLH in Animal Models

• Following Olsson’s demonstration of significant reduction in BT recurrence with ID KLH immunization, animal studies have consistently demonstrated and confirmed the anti-tumor efficacy of KLH. In summary:
  – Pre-immunization and intralesional KLH inhibits transplanted bladder cancer
  – Endotoxin enhances the efficacy of KLH
  – Combination therapy, eg KLH plus IL-2, Ifn alpha or Ifn gamma improves response: as high as 100% with Interferon alpha +KLH
  – Minimal dose/response relationship exists
  – Minimal toxicity observed

• Local immune response and anti-tumor effect is confirmed, but what about the **systemic** effect reported by Olsson?
Immunotherapy of Murine Bladder Cancer (MBT2) Using Immunotheel KLH Derivative Without Pre-Immunization
(Treatment Days = 1, 3, 5, 7, 9, 11, and 14)
Immunotherapy of Murine Bladder Cancer (MBT2) Using Immucothel KLH Derivative Without Pre-Immunization

(Treatment Days = 1, 3, 5, 7, 9, 11, and 14)
Immunotherapy of Murine Bladder Cancer Using KLH and LPS

- High LPS
- Purified KLH
- Crude KLH
- pKLH + LPS
- Low LPS
- Saline
- BCG

Graph showing tumor incidence over days from tumor transplantation.
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  – Pre-immunization and intralesional KLH inhibits transplanted bladder cancer
  – Endotoxin enhances the efficacy of KLH
  – Combination therapy, eg KLH plus IL-2, Ifn alpha or Ifn gamma improves response: as high as 100% endotoxin + purified KLH
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  – Minimal toxicity observed

• Local immune response and anti-tumor effect is confirmed, but what about the systemic effect reported by Olsson?
Evidence of *Systemic* KLH Immunity to Bladder Cancer

- BBN 0.05% in drinking water: bladder cancer model in rats.
- 1mg KLH s.c. plus 12.5 intraves significantly reduces BT formation.*
- Pre-sensitization 1mg KLH followed by twice weekly 1mg SC or 12.5mg intraves beginning on day 15: 50% tumor in SC group compared with 74% in the intravesical group!**

*Recker and Rubben, 1989  **Linn and Rubben et al., 1998
Hemocyanin

Clinical Studies
KLH Uncontrolled Trials

- 548 patients with Ta, T1, T2 TCC or CIS followed for an average of 21.5 months
- 28.5% recurrence at 21.5 months
- **CIS**: Jurincic’1995: 52% CR (11/21)
- **CIS**: Bassi’2000: 50% CR (14/28)
- **CIS**: Lamm’2000: 50% CR (9/18) CIS alone plus 33% (4/12) in CIS plus papillary TCC
<table>
<thead>
<tr>
<th>Stage</th>
<th>CR (N)</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS</td>
<td>9</td>
<td>50%</td>
</tr>
<tr>
<td>Ta, T1, CIS</td>
<td>4</td>
<td>33%</td>
</tr>
<tr>
<td>Ta, T1</td>
<td>3</td>
<td>20%</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>36%</td>
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Side Effects of KLH in 54 Evaluable Patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>KLH</th>
<th>*BCG</th>
</tr>
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<tbody>
<tr>
<td>Dysuria</td>
<td>24%</td>
<td>60%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>7%</td>
<td>26%</td>
</tr>
<tr>
<td>Malaise</td>
<td>7%</td>
<td>33%</td>
</tr>
</tbody>
</table>

*Contemporary series
## KLH in CIS/Residual Papillary Papillary TCC

<table>
<thead>
<tr>
<th>Dose</th>
<th>CR (N)</th>
<th>CR (%)</th>
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</thead>
<tbody>
<tr>
<td>0.4 mg</td>
<td>4</td>
<td>29%</td>
</tr>
<tr>
<td>2.0 mg</td>
<td>8</td>
<td>42%</td>
</tr>
<tr>
<td>10 mg</td>
<td>4</td>
<td>29%</td>
</tr>
<tr>
<td>50 mg</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Total:</td>
<td>22</td>
<td>34%</td>
</tr>
</tbody>
</table>

No dose/response observed. All patients received the same 1mg dose of S.C. KLH!
### KLH in Refractory TCC

<table>
<thead>
<tr>
<th>Dose</th>
<th>CR (N)</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 mg</td>
<td>1</td>
<td>25%</td>
</tr>
<tr>
<td>2.0 mg</td>
<td>3</td>
<td>30%</td>
</tr>
<tr>
<td>10 mg</td>
<td>3</td>
<td>30%</td>
</tr>
<tr>
<td>50 mg</td>
<td>2</td>
<td>29%</td>
</tr>
<tr>
<td>Total:</td>
<td>9</td>
<td>26%</td>
</tr>
</tbody>
</table>
KLH Controlled Clinical Trials

- 393 patients in 8 trials; 188 KLH, 205 other
- KLH: 25.7% recurrence, 21.1 months, versus 41.0% recurrence with chemo, TUR, or BCG
- BCG: 14% rec. (3/21) vs. 41% (7/17) KLH
- MMC: 33% (21/64) vs. 13% (9/71), p<0.01
- KLH vs. Chemo/non- BCG: 24% vs 44% rec.
## KLH vs Mitomycin C

<table>
<thead>
<tr>
<th>Author/yr</th>
<th>N</th>
<th>KLH</th>
<th>% rec</th>
<th>MMC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klippel’85</td>
<td>50</td>
<td>3/30 (10%)</td>
<td>(20%)</td>
<td>4/20</td>
<td>NS</td>
</tr>
<tr>
<td>Jurincic’88</td>
<td>44</td>
<td>3/21 (14%)</td>
<td>(39%)</td>
<td>9/23</td>
<td>0.05</td>
</tr>
<tr>
<td>Al-Naieb’90</td>
<td>41</td>
<td>3/20 (15%)</td>
<td>(38%)</td>
<td>8/21</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td>135</td>
<td><strong>9/71 (13%)</strong></td>
<td>(33%)</td>
<td><strong>21/64</strong></td>
<td><strong>0.01</strong></td>
</tr>
</tbody>
</table>
What is the Future of Hemocyanins in Bladder Cancer?

• Systemic efficacy in bladder cancer was first reported in 1974 by Olsson and HAS BEEN CONFIRMED IN ANIMAL MODELS!

• Percutaneous hemocyanin appears to be effective in CIS, and therefore may be effective in upper tract TCC

• Hemocyanin should be tried as an adjuvant to cystectomy- with or without chemotherapy!
Conclusions

• Hemocyanins have a broad range of beneficial immune effects, both cellular and humoral

• KLH is clearly effective in the prevention and treatment of bladder cancer

• Unlike BCG, KLH appears to have a very significant systemic effect

• While hemocyanins may be less effective than BCG in the treatment of local TCC, they are clearly less toxic
Conclusions

• Hemocyanins, like other immunotherapies, appear to be more effective when used in combination with other immunotherapy

• With a systemic effect:

• Hemocyanins should be studied as an adjuvant to the treatment of upper tract TCC

• Hemocyanins should be studied as an adjuvant to cystectomy.
Thanks,
Don Lamm, Phoenix

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