Laboratory and Clinical Experience with Keyhole limpet hemocyanin (Immucothel) in Superficial Bladder Cancer
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Laboratory and Clinical Experience with Keyhole limpet hemocyanin (Immucothel®) in Superficial Bladder Cancer

D. L. Lamm

BCG has been found to be more effective in cases with marker lesions of transitional cell carcinoma, inducing 61 % complete response rates compared to 38-53 % by chemotherapy. Similar results were obtained in the treatment of carcinoma in situ (72 % complete remissions vs. 38-53 %). Time to recurrence at five years showed 45 % of patients free of disease after BCG versus 18 % treated with chemotherapy. Keyhole limpet hemocyanin (KLH), which is now commercially available as Immucothel®, provides a very safe and effective immunotherapeutic alternative for the treatment of superficial bladder cancer. To define the role of KLH in the management of superficial bladder cancer and identify its appropriate place in the therapeutic armamentarium, the results expected with intravesical chemotherapy, the results expected with intravesical BCG immunotherapy, and the advantages and limitations of KLH will be reviewed.

The primary treatment of superficial bladder cancer is transurethral resection, but despite resection, up to 86 % of patients will have tumor recurrence within 15 years [1]. Intravesical chemotherapy is used to reduce the risk of tumor recurrence. However, the relative benefit of chemotherapy is quite modest. Intravesical chemotherapy reduces tumor recurrence rate compared with surgery alone by about 20 % within the first two years, but with further follow-up by five years the reduction in tumor recurrence is only 7 % [2]. More importantly, intravesical chemotherapy does not reduce disease progression [3, 4]. BCG immunotherapy is relatively more effective than chemotherapy. BCG reduces tumor recurrence by 40 % in the first two years, and by as much as 20 % at five years. However, BCG immunotherapy has significant side effects and up to 60 % of patients will eventually fail to respond to BCG [5–7]. Clearly, more effective treatments are needed.

Intravesical Chemotherapy – BCG Immunotherapy

The relative efficacy of intravesical chemotherapy and BCG immunotherapy can be observed in the reported complete response rates of the treatment of existing disease (marker lesion). With papillary tumors, thiopeta produces a complete response rate of 34 %, compared with 42 % of patients treated with doxorubicin and 47 % of patients treated with mitomycin C. BCG has produced a 61 % complete response rate in the treatment of papillary disease [8]. In carcinoma in situ, reported complete response rates of chemotherapy with thiopeta are 38 %, with doxorubicin 48 %, and with mitomycin C 53 %. BCG therapy results in a 72 % complete response rate in carcinoma in situ. In our review of over 2000 patients entered in controlled intravesical chemotherapy trials, the average reduction in disease recurrence in patients treated with chemotherapy compared with surgery alone was 17 %. Only 17 of these 32 controlled trials achieved statistical significance at a p level less than 0.05. In contrast, in seven controlled BCG trials, all seven achieved statistical significance of less than 0.05, and the average reduction in tumor recurrence was 44 % (Table 1).

The advantage of immunotherapy with BCG relative to chemotherapy is illustrated in the time to recurrence of the Southwest Oncology Group study comparing BCG and doxorubicin. At five years follow-up, 37 % of patients with papillary tumors were stage TaT1 or disease-free when treated with BCG, compared with only 17 % of those treated with doxorubicin. In patients with carcinoma in situ, the difference was more dramatic: 45 % of BCG treated patients were disease-free at five years compared with 18 % of those treated with doxorubicin [8, 9]. These data compare very favorably with the results of intravesical chemotherapy. In the EORTC/MRC meta-analysis of over 2500 patients, by five years the reduction in tumor recurrence with chemotherapy was only 6 %.

Regarding disease progression chemotherapy data are even more discouraging [2, 3, 10]. There is no reduction in
null
The successful randomized KLH clinical trials again sparked our interest in KLH and we resumed our laboratory studies. In a series of experiments comparing increasing doses of various KLH preparations with BCG and saline treated controls in the murine bladder cancer model [18, 19] we found that KLH resulted in statistically significant (p < 0.001) reduction in tumor incidence, tumor growth, and animal mortality. Crude KLH preparations, which contain endotoxin, appeared to be more effective than purified endotoxin-free KLH. Our studies of endotoxin alone demonstrated that endotoxin had definite anti-tumor activity (Tables 2, 3) [11, 12].

As with other immunotherapies, we found that KLH had a bell-shaped dose-response curve with intermediate doses being the most effective. The addition of small amounts of endotoxin to purified KLH greatly enhanced the anti-tumor effects. In fact, KLH plus a low dose (100 units) of endotoxin produced complete protection from tumor transplantation and was significantly better than BCG immunotherapy. Large amounts of endotoxin, however, reduced efficacy, again illustrated by bell-shaped dose-response curve. The optimal response to KLH occurred when animals were preimmunized to KLH. Studies of the immune response to KLH [19–21] showed that natural killer cell activity is stimulated with repeated KLH immunizations (p < 0.003) and IgG and IgM antibodies to KLH are induced in the mouse, but these antibody titers are not directly correlated with KLH antitumor activity. These studies suggested that refinement of KLH immunotherapy might result in a treatment that was at least as good, and potentially superior to BCG immunotherapy.

Based on these successful in-vivo studies, we initiated a dose-escalation clinical phase I/II KLH trial in patients with carcinoma in situ or residual papillary transitional cell carcinoma. All patients received 1 mg of percutaneous KLH two weeks prior to intravesical instillation. They then received intravesical KLH in doses of 0.4, 2, 10, or 50 mg. Patients who had incomplete response were eligible for escalation to the next dose level. In 54 evaluable patients we observed minimal side effects with KLH instillation: 24 % had mild dysuria; 7 % hematuria; and 7 % malaise. These results compare very favorably with contemporary series of BCG immunotherapy that results in 60 % dysuria, 26 % hematuria, and 33 % malaise. Complete responses were observed at all dose levels. Complete response was seen in 20 % of patients receiving 0.4 mg KLH, 42 % in patients receiving 2.0 mg, 29 % in patients receiving 10 mg, and 35 % in patients receiving 50 mg for an overall complete response rate of 34 %. In patients with BCG refractory residual papillary transitional cell carcinoma complete responses were 25 % in those receiving 0.4 mg, 30 % at 2 mg, 30 % at 10 mg, and 29 % at 50 mg for overall response rate of 26% (Table 4) [11, 12]. Nine of 18 patients with carcinoma in situ without associated Ta or T1 transitional cell carcinoma had complete response (50 %). These data again confirm the efficacy of KLH in the treatment of carcinoma in situ and residual or refractory stage Ta/T1 transitional cell carcinoma. As in BCG therapy, response rates are higher in patients with CIS than those with residual papillary disease [22].

Conclusions
Immunotherapy has distinct advantages over chemotherapy in the treatment of superficial bladder cancer. Three decades of experience with BCG immunotherapy has resulted treatment that is highly effective, but the side effects of BCG are significant and many patients become refractory or intolerant to BCG. KLH is confirmed to be an effective alternative immunotherapy and is associated with minimal toxicity. KLH therapy, therefore, would appear to be an ideal treatment for intermediate or even low risk bladder tumor patients (Ta, T1, G1–2). This philosophy would spare many patients the side effects of BCG. Importantly, KLH would offer a therapeutic option in patients who are intolerant or refractory to BCG.

Further research is necessary to identify the optimal dose and schedule of KLH immunotherapy. Additional research will also be needed to determine if KLH results in protection from disease progression, as seen with BCG therapy.

References

Table 2. Comparison of animal survival after treatment with BCG, crude KLH and purified KLH (BCG = Bacillus Calmette Guerin, Crude KLH = non purified KLH, KLH = Keyhole Limpet Hemocyanin, Im 50 = Immunothel = modified and purified KLH)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Volume, mm³</th>
<th>Survival, %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>71 ± 111</td>
<td>90</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Crude KLH</td>
<td>233 ± 476</td>
<td>100</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Im 50</td>
<td>752 ± 194</td>
<td>90</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Saline</td>
<td>3362 ± 1887</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. KLH and endotoxin interaction in MBT-2 mouse model (BCG = Bacillus Calmette Guerin, KLH = Keyhole Limpet Hemocyanin, EU = endotoxin units)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Volume, mm³</th>
<th>p-value</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>5200 ± 700</td>
<td>8</td>
<td>58</td>
</tr>
<tr>
<td>BCG</td>
<td>1500 ± 550</td>
<td>&lt;0.0001</td>
<td>58</td>
</tr>
<tr>
<td>KLH</td>
<td>590 ± 410</td>
<td>&lt;0.001</td>
<td>92</td>
</tr>
<tr>
<td>KLH + 100 EU</td>
<td>0 ± 0</td>
<td>&lt;0.0001</td>
<td>100</td>
</tr>
<tr>
<td>KLH + 1000 EU</td>
<td>370 ± 300</td>
<td>&lt;0.0001</td>
<td>50</td>
</tr>
<tr>
<td>100 EU</td>
<td>2000 ± 660</td>
<td>&lt;0.0004</td>
<td>42</td>
</tr>
<tr>
<td>1000 EU</td>
<td>1100 ± 470</td>
<td>&lt;0.0001</td>
<td>58</td>
</tr>
</tbody>
</table>

* p = 0.012, sign. better than BCG

Table 4. Complete response rates after adjuvant treatment with KLH in patients with refractory transitional cell carcinoma (CR = complete remission).

<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>

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