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

D. L. Lamm

BCG wirkt bei Markerläsionen des Transitionalzellkarzinoms stärker und erreicht 61 % Response-Raten, verglichen mit 38–53 % bei Chemotherapie. Ähnliche Ergebnisse liegen auch beim Carcinoma-in-situ vor: 72 % Komplettremissionen vs. 38–53 %. Nach 5 Jahren sind 45 % der Patienten nach BCG-Behandlung krankheitsfrei, gegenüber 18 % nach Chemotherapie. Keyhole limpet Hämocyanin (KLH) wurde bereits in den 1960er Jahren als Immunmodulator getestet und induziert eine deutliche Reduktion beim Blasenkrebs von 6,4 Rezidiven pro 100 Patientenmonaten vor KLH-Gabe auf 1,9 nach KLH. Diese Ergebnisse wurden durch eine kontrollierte Studie an 19 Patienten bestätigt, bei der in der Kontrollgruppe 70 % Rezidive auftraten, verglichen mit 11 % in der KLH-Gruppe. Weitere experimentelle und klinische Studien kamen zu ähnlichen Ergebnissen. KLH in der hochgereinigten Form von Immucothel erwies sich als ebenso wirksam wie die Chemotherapie bei weniger unerwünschten Ereignissen. Die Immuntherapie als adjuvante Therapie bei superfiziellen Blasenkrebs nach Resektion wird als Dauertherapie über 10 Monate mit einer monatlichen Instillation nach einer initialen Phase über 6 Wochen mit wöchentlichen Instillationen durchgeführt.

*BCG has been found to be more effective in cases with marker lesions of transitional cell carcinoma, inducing 61 % of complete response rates compared to 38–53 % by chemotherapy. Similar results were obtained in the treatment of carcinoma in situ (72 % complete remissions versus 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, first tested as an immunomodulator in the 1960's, induced a marked reduction in bladder carcinoma from 6,4 recurrences per 100 patients months before KLH to only 1,9 after KLH. This was confirmed by a controlled study of 19 patients. In the control group 70 % of patients had tumor recurrence compared to only 11 % in the KLH group. These results were further confirmed by experimental studies and by several clinical trials. KLH in the purified form of Immucothel was shown to be as effective as chemotherapy but with much less adverse effects. A main point of immunotherapy as adjuvant treatment of superficial bladder cancer after resection is the necessity of maintenance therapy for 10 months with monthly instillations after an initial treatment of 6 weeks with weekly instillations. *J Urol Urogynekol (Österreich) 2003; 10 (2): 18–21.**

Keyhole limpet hemocyanin (KLH), which is now commercially available as Immucothel® (biosyn Arzneimittel GmbH, 70734 Fellbach, Germany) 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 88 % 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, thiotepa 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 thiotepa 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

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Table 1. Controlled BCG trials (No = patient number, NoRx = relapses after operation, BCG = relapses after BCG, BEN = median reduction of relaps rate)

Author	No.	No. Rx	BCG	BEN.	p
Lamm 1985 [23]	57	52 %	20 %	32 %	< 0.001
Herr 1985 [24]	86	95 %	42 %	53 %	< 0.001
Herr 1988 (CIS) [25]	49	100 %	35 %	65 %	< 0.001
Yamamoto 1990 [26]	44	67 %	17 %	50 %	< 0.05
Pagano 1991 [27]	133	83 %	26 %	57 %	< 0.001
Mekelos 1993 [28]	94	59 %	32 %	27 %	< 0.02
Krege 1996 [29]	224	48 %	29 %	24 %	< 0.05
Total	687	72 %	28 %	44 %	

disease progression with chemotherapy and even a suggestion that these patients may be at increased risk of progression.

Controlled randomized trials of BCG immunotherapy versus chemotherapy have shown a consistent advantage of BCG when compared with thiotepa and doxorubicin. The advantage of BCG versus mitomycin C, however, has not been consistently proven. This is surprising since controlled comparisons of chemotherapies have failed to show any advantage of mitomycin C over other intravesical chemotherapies. This inconsistency may relate to the schedules of BCG used in some of these studies. When maintenance BCG schedules are used, as illustrated in the Southwest Oncology Group study no 8795 (Figure 1), a consistent advantage of BCG over mitomycin C is seen.

Maintenance Immunotherapy

Maintenance immunotherapy appears to be an important principle of immunotherapy and shows a significant difference compared to chemotherapy. Southwest Oncology Group protocol 8507 compared six-week induction BCG with induction BCG plus three-weekly maintenance over the period of three years. In that study, tumor recurrence in patients with high risk papillary disease was reduced from 52 % at ten years to only 25 % in patients receiving BCG maintenance ($p < 0.0001$). Progression, defined as stage progression to T2 or greater, or the requirement for cystectomy, radiation therapy, or systemic chemotherapy, was reduced by 8 % with the use of maintenance BCG ($p < 0.04$) [11, 12].

Further supporting the importance of maintenance in immunotherapy protocols is the meta-analysis reported by Sylvester et al [13]. In an analysis of 24 trials containing progression information on 4863 patients, 78 % (20) of 24 trials used maintenance BCG. Overall progression was reduced from 13.8 % in arms that did not receive BCG to 9.8 % in arms that received BCG (odds ratio 0.73; p value 0.001). The effect of BCG was similar in both papillary and carcinoma in situ patients. Importantly, BCG was only effective in reducing progression in trials where maintenance was used. When maintenance BCG was used, the risk of disease progression was reduced by 37 % ($p = 0.00004$). There was no reduction in progression without the use of maintenance BCG. It is clear from these data that immunotherapy provides significant advantages over chemotherapy in the treatment of superficial bladder cancer. An important question remains to be answered: Can the advantages of immunotherapy be obtained without the significant side effects that occur in BCG therapy?

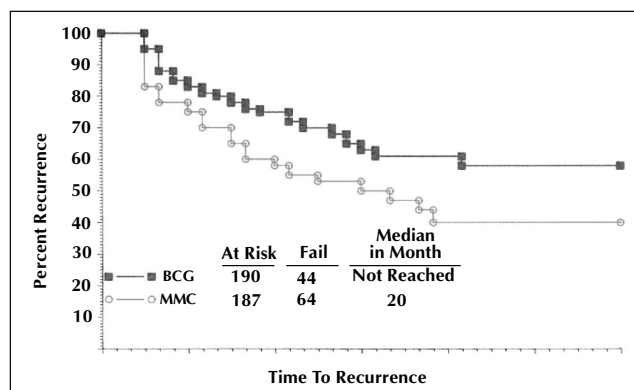


Figure 1. BCG versus mitomycin C (SWOG 8795): time to tumor recurrence.

Keyhole limpet hemocyanin

Beginning in the 1960's, KLH was used as a monitor of immune reactivity. In 1974 Olsson reported his experience with a study designed to demonstrate that patients with impaired cellular immunity were at increased risk for bladder tumor recurrence and progression [14]. In this study, he gave to bladder tumor patients a sensitizing dose of 5 mg KLH followed by a testing dose of 100 mcg. He observed, however, a marked reduction in tumor recurrence in all patients vaccinated. The rate of tumor recurrence was reduced from 6.4 recurrences per 100 patient months before KLH to only 1.9 after KLH. This was confirmed by a controlled study of 19 patients. In controls, 70 % of patients had tumor recurrence compared to only 11 % recurrence in patients treated with KLH [14]. It is important to notice that the reported benefit of KLH in these original studies occurred with systemic administration alone, without intravesical instillation.

Impressed by these reports, we initiated laboratory studies of KLH in the murine bladder tumor model. Using a sensitizing dose of 200 mcg of KLH followed by 50 mcg intravesically one and seven days after tumor transplantation, significant reduction in tumor growth and prolongation of survival was observed ($p < 0.01$) [15]. Our mouse bladder cancer model studies of KLH confirmed the preliminary clinical experience that KLH was an effective immunotherapy for bladder cancer. However, the magnitude of this protective immune response in the bladder cancer model was less than we had observed with BCG immunotherapy. We therefore directed our efforts to further studies of BCG immunotherapy.

In Europe, laboratory and clinical trials of KLH continued and in 1988, Jurincic and associates published a randomized comparison of Immunothel® and mitomycin C chemotherapy [16]. In 44 randomized patients, mitomycin C resulted in a 39 % recurrence rate (9.3 recurrences per 100 patient months) compared with only 14 % recurrence rate (3.3 recurrences per 100 patient months) with immunotherapy using 10 mg of intravesical KLH. Flamm and associates compared 20 mg KLH with intravesical Epodyl [17]. In 84 randomized patients, recurrence occurred in 35 % of patients treated with Epodyl compared with 21 % of patients treated with KLH. These clinical trials clearly demonstrated the efficacy of KLH in bladder tumor prophylaxis. Moreover, side effects with KLH were found to be minimal.

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 29 % 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

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 = Immucothel = modified and purified KLH)

Treatment	Volume, mm ³	Survival, %	p-value
BCG	71 ± 111	90	< 0.05
Crude KLH	233 ± 476	100	< 0.05
Im 50	752 ± 194	90	< 0.05
Saline	3362 ± 1887	30	

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

Treatment	Volume, mm ³	p-value	Survival, %
Saline	5200 ± 700		8
BCG	1500 ± 550	< 0.0001	58
KLH	590 ± 410	< 0.0001	92
KLH + 100 EU	0 ± 0	< 0.0001*	100
KLH + 1000 EU	370 ± 300	< 0.0001	50
100 EU	2000 ± 660	< 0.0004	42
1000 EU	1100 ± 470	< 0.0001	58

* $p = 0.012$, sign. better than BCG

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

Dose	CR (n)	CR (%)
0.4 mg	1	25
2.0 mg	3	30
10 mg	3	30
50 mg	2	29
Total	9	26

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.

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