招請講演

Bacillus Calmette-Guerin Immunotherapy of Superficial Bladder Cancer

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Bacillus Calmette-Guerin was first used clinically as a vaccine for tuberculosis in France in 1921. The success of BCG spread rapidly, and in 1925 BCG was introduced in Japan. The profound stimulation of the immune system resulting from administration resulted in evaluation of BCG in the treatment of cancer. Despite the checkered past of BCG immunotherapy in other cancers, intravesical BCG immunotherapy is now recognized to be the treatment of choice for carcinoma in situ of the bladder and is considered by most to be the most effective prophylactic treatment for patients with aggressive superficial transitional cell carcinoma. While the mechanism of action of BCG is incompletely defined, it is recognized as a potent nonspecific immune stimulant. Intravesical BCG induces infiltration of a broad range of inflammatory and immune cells in the lamina propria of the bladder, and activates macrophages, T and B lymphocytes, natural killer cells and a variety of other immune surveillance mechanisms including lymphokine and interferon production.

Multiple studies, as illustrated in table 1, have demonstrated that BCG prophylaxis markedly reduces tumor recurrence when compared to surgi-

cal resection alone, and several studies suggest that, unlike chemotherapy, protection from tumor recurrence lasts for at least 5 years. Importantly, long term reduction in tumor recurrence appears to be associated with a reduction in tumor progression in patients treated with BCG. In two studies, as illustrated in Table 1, statistically significant reduction in tumor progression occurred in BCG treated patients, and overall progression was reduced from 23% in patients treated with surgery alone to 13% in those treated with adjuvant BCG ($p < 0.03$). Controlled randomized studies of BCG immunotherapy and intravesical chemotherapy, as illustrated in Table 2, have shown that BCG provides superior protection from tumor recurrence when compared with thiotepa, doxorubicin, and mitomycin. In 9 randomized comparison studies, BCG was found to result in significantly fewer recurrences in all comparisons with thiotepa and doxorubicin and 2 of 5 comparisons with mitomycin. Overall, tumor recurrence was reduced from an average of 43% with chemotherapy to 25% with BCG.

BCG immunotherapy is particularly effective in transitional cell carcinoma in situ. Complete response to intravesical chemotherapy in carcinoma

Table 1 Tumor Recurrence and Progression in Controlled Studies

Agent	Number pts/series/sig	Recurrence			Progres.		
		Control	Treated	Benefit	C	RX	Dif
Thiotepa	1007/10/6	56%	44%	12%	6%	4%	NS
Doxo.	1241/5/3	47%	34%	13%	8%	9%	NS
Mitomycin	1157/6/2	50%	35%	15%	7%	4%	NS
BCG	496/5/4	72%	32%	40%	23%	13%	03

Illustrated are a comparison of relative benefits of intravesical chemotherapy and immunotherapy with respect to reduction in tumor recurrence and progredssion vs surgery alone.

Table 2 Recurrence in Controlled Comparison Trials

Study	BCG	Thio	Dox	MMC	P level
Brosman, '82	0	47%			<0.01
Netto, '83	7%	43%			<0.01
Martinez, '90	13%	36%	43%		<0.01
Thiotepa ave :	7%	42%			
SWOG, '91	63%		83%		<0.02
Doxorubicin ave :	38%		63%		
Debruyne, '88	30%			25%	NS
Finnblad, '90	28%			62%	<0.01
Rubben, '90	35%			35%	NS
Witjes, '93	29% (RIVM)			26%	NS
	34% (Tice)				NS
SWOG, '93	20%			33%	<0.01
Mitomycin ave :	29%			36%	
BCG ave	25%		Chemotherapy ave : 43%		

in situ ranges from 38% to 53% for thiotepa and mitomycin, respectively. Despite these significant response rates, intravesical chemotherapy has not been demonstrated to alter the long term aggressive natural history of CIS, and in general fewer than 20% of patients remain disease free for 5 years. The overall complete response rate of CIS to BCG is now over 70%. The Southwest Oncology Group comparison of Connaught BCG and doxorubicin is representative of the excellent long term result of BCG in the treatment of CIS. (Lamm, 1992) In that study of 112 patients with CIS randomized to doxorubicin chemotherapy or BCG immunotherapy, complete response was documented in 34% of patients in the doxorubicin arm and 70% in the BCG arm. By 5 years only 18% in the doxorubicin arm remained disease free, compared with 45% in the BCG arm ($p < 0.001$), of the patients who had complete response to BCG, 64% maintained that complete response for 5 years. Compared with the historical natural history that shows 54% of patients with CIS will have progression to invasive disease within 5 years (Lamm, 1992), these are remarkable results.

Recent data suggest that improved treatment schedules can further improve the results of BCG immunotherapy. The Southwest Oncology Group registered 660 patients in randomized comparison of the standard 6 week BCG induction treatment with a maintenance regimen. In 218 patients with CIS, 3 additional induction BCG treatments at 12 weeks increased the complete response from the expected

73% to 87% ($p < 0.04$). (Lamm, 1994) Considering only patients who had complete response at 3 months, maintenance BCG treatment using 3 weekly treatments at 12 weeks, 6 months and every 6 months to 3 years increased the long term complete response from the expected 65% to 83% ($p < 0.04$). In disease free patients with rapidly recurring or aggressive stage Ta, T1 transitional cell carcinoma, the advantage of maintenance BCG was even more dramatic, increasing the long term disease free status from the expected 50% to 83% ($p < 0.000001$).

Conclusions : BCG immunotherapy heralds a new era in the management of superficial bladder cancer. Unlike chemotherapy, BCG appears to produce a long term protection from tumor recurrence and disease protection. These effects are now translated into an improvement in survival. Maintenance BCG, using three weekly treatments at 3 months, 6 months and every 6 months provides even further significant improvement in results, and can now be recommended as the standard to which other treatments must now be compared.

References:

- 1) Lamm DL and Griffith JG : Intravesical therapy : Does it affect the natural history of superficial bladder cancer? *Semin Urol* 10 : 39, 1992.
- 2) Lamm DL : Carcinoma in situ, In *Superficial Bladder Cancer*, *Urol Clinics of N Amer* DL Lamm, ed. Volume 19, pp 499—508, August, 1992.