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INTRACAVITARY BACILLUS CALMETTE-GUERIN IN THE TREATMENT OF SUPERFICIAL BLADDER TUMORS

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ABSTRACT

Patients with recurrent superficial bladder tumors have been treated by vesical and intradermal administration of Bacillus Calmette-Guerin. The pattern of recurrence in 9 patients has been altered favorably. Although the findings are still preliminary they appear to hold promise of a new therapeutic approach to the treatment of a group of neoplasms for which effective therapy is still lacking.

Instillation of oncolytic agents has been used for many years in the treatment and prophylaxis of superficial bladder tumor recurrences with variable success.[1–3] The location and natural history of these neoplasms and the easy accessibility of the bladder make this type of therapy particularly attractive.

The antigenicity of bladder tumors has been demonstrated repeatedly.[4,5] This would suggest that immunotherapy may be useful in the eradication of non-invasive bladder neoplasms. Successful Bacillus Calmette-Guerin (BCG) immunotherapy must meet several criteria: 1) ability to develop an immune response to mycobacteria antigens, 2) adequate numbers of living bacilli, 3) close contact between BCG and tumor, 4) relatively small tumor load and 5) freedom from major systemic side effects.[6] Superficial bladder tumors appear to be ideally suited to this approach. The results presented summarize our initial experience with the use of BCG in the treatment and prophylaxis of these neoplasms.

MATERIALS AND METHODS

There were 2 groups of patients considered candidates for BCG immunotherapy. In group 1 were patients with a history of persistent tumor recurrences but in whom all gross evidence of cancer was eliminated by endoscopic fulguration prior to the onset of immunotherapy. In group 2 were patients with tumor recurrence in whom complete endoscopic eradication of the neoplasm was not achieved. In every case the tumor was clinically and histologically staged and considered to be superficial (T_0 to T_1).

Immunological evaluation was performed in vivo and in vitro. In vivo studies consisted of the determination of delayed cutaneous hypersensitivity to a battery of recall antigens: tuberculin, histoplasmin, dermatophytin and streptokinase-streptodornase. In vitro studies included absolute peripheral lymphocyte counts and determination of T and B subpopulations as previously described.[7]

BCG administration. The vaccine was given by intradermal and per urethram routes. Five mg. BCG (Institut Armand Frappier, Montreal) was administered to the upper thigh using a multiple puncture apparatus. For the intracavitary administration 120 mg. of the vaccine reconstituted in 50 cc normal saline was injected into the bladder through a No. 8 urethral catheter. The patient was advised to retain the fluid for not less than 2 hours. Treatments were repeated at weekly intervals for 6 weeks, alternating thighs for the intradermal administration.

Four to 6 weeks after the last immunization cystoscopy was performed. Any areas suggesting the presence of tumor was biopsied, otherwise random samples were taken. Recheck cystoscopies were performed periodically thereafter.

RESULTS

Delayed cutaneous hypersensitivity. All patients exhibited cutaneous reaction to mycobacteria antigens. In 4 cases the administration of tuberculin caused no reaction but strong reactivity was obtained 3 weeks after administration of BCG. Response to other recall antigens was found in 6 patients, the most common being to streptokinase-streptodornase. All patients tested with dinitrochlorobenzene showed reactivity to this substance.

Quantitative lymphocyte studies. The mean numbers of absolute peripheral lymphocytes and the T and B subpopulations are illustrated in figure 1. The initial values are not different from the ones found in normal subjects. This finding may well reflect the limited tumor load. Although an increase in lymphocyte populations was noted after the onset of therapy the values lack statistical significance.

Recurrence rate. The number of recurrences found in the 12-month period immediately before BCG therapy and during the post-vaccination period is illustrated in table 1. Before therapy 9 patients demonstrated a total of 22 recurrences during 77 patient months. After vaccination these 9 patients yielded 1 recurrence during a followup of 41 patient months. However, these 2 total distributions do not permit a valid statistical analysis. On the other hand, looking at 5 cases in which the pre-BCG and post-BCG periods were identical (25 patient months), it was found that 12 recurrences were detected during the pre-BCG period, while after immunization no recurrences were present. With the chi-square test in these 5 patients for the pre-BCG versus the post-BCG periods, a statistically significant difference was obtained (p less than 0.01).

Of the 9 patients who have now received BCG immunotherapy 5 were treated for prevention of recurrence and 4 for residual tumor.

CASE REPORTS

Case 1. An 80-year-old man was found to have a transitional cell carcinoma of the bladder in 1970. Elimination of tumor was achieved by endoscopic fulguration but rechecks every 4 months demonstrated persistent recurrences. In

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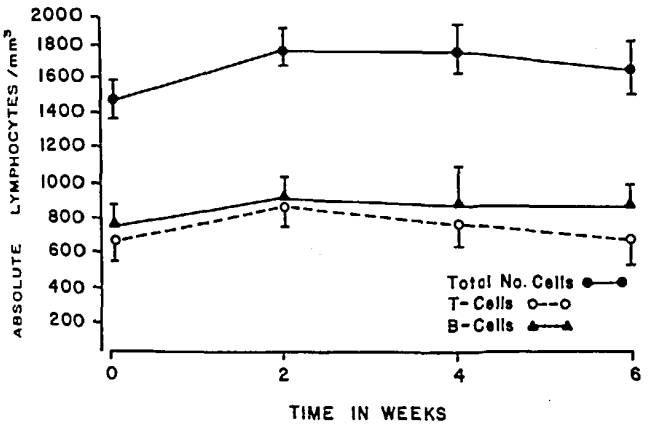

FIG. 1. Absolute numbers (plus or minus 1 standard error of means of circulating lymphocytes, and T and B subpopulations from onset of therapy.

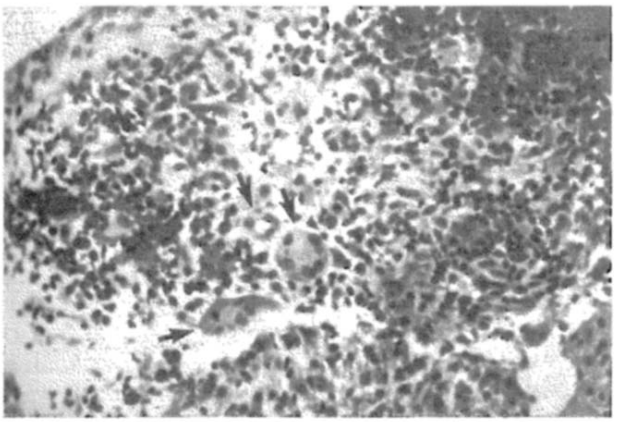

FIG. 2. Granulomatous reaction seen in biopsy of bladder. Arrows indicate giant cells.

June 1974 a course of intradermal and intracavitary BCG was decided upon after conversion to purified protein derivative positive intradermal injection of BCG. It was well tolerated although the patient experienced fever, malaise and dysuria for 48 to 72 hours after the vaccination. After immunotherapy no recurrences have been detected endoscopically and random biopsies have failed to show neoplastic changes in the mucosa (table 2, patient 4). The patient has been free of tumor for 13 months.

Case 2. A 54-year-old man with a strong family history of bladder cancer was found to have a tumor immediately above the left ureteral orifice. Because of the location and size of the neoplasm he was treated by open excision and diathermy. The tumor was superficial and well differentiated but random samples taken at a distance from the lesion showed epithelial dysplasia. At 3 months no recurrence was seen but the mucosa had a patchy "angry" looking appearance. Three months later 5 small recurrences were detected, 4 of which were fulgurized and 1 of which was biopsied. The patient then received immunotherapy. Ten weeks after termination of the trial cystoscopy was done. No evidence of tumor was found except for the presence of a lesion with the gross appearance suggestive of severe inflammation. The lesion, which was located at the site of the previous recurrence that had been dealt with by biopsy only, was treated by excisional biopsy. Histological examination disclosed a granuloma with multinucleated giant cells, lymphocytes and plasma cell infiltration (fig. 2, table 2, patient 5). Repeat cystoscopy 22 weeks after completion of therapy revealed no recurrence.

Case 3. A 55-year-old woman was found to have a well-differentiated superficial transitional cell carcinoma of the bladder, which was successfully removed endoscopically in 1962. Multiple superficial recurrences were found on repeated endoscopies during the ensuing 18 months. In the early part of 1964 the patient was given a course of thio-tepa, which rendered her free of tumor for 9 months, at the end of which further persistent recurrences were found. After a second course of thio-tepa prevention of tumor recurrence was achieved for another 9 months. However, at the beginning of 1969 recurrences were again noted. A third course of thio-tepa proved totally unsuccessful. Multiple recurrences were found persistently at 3-month intervals. In June 1972 the patient was started on a fourth course of thio-tepa followed by monthly instillations of the drug. This regimen kept her free of tumor until December 1973 when new tumors were detected. Twelve instillations of epodyl failed to prevent additional recurrences. In February 1975 the immunotherapy trial was begun. During therapy symptoms of cystitis and low grade fever developed for 2 days after each instillation. Three months after completion of the bladder instillations cystoscopy was done. Biopsy showed patchy areas of mucosal inflammation and necrosis associated with granulomatous inflammation, multinucleated giant cells of the Langhan's type and histiocytes (table 2, patient 6). Cystoscopy 6 months later did not reveal tumor recurrence.

Case 4. A 72-year-old man had a transitional cell carcinoma located at the vault of the bladder for which he underwent partial cystectomy in June 1971. For the next 18 months persistent recurrences were detected at the bladder vault. Since a cardiac condition precluded a major operation the patient received 5,500 rads cobalt therapy, which failed to eliminate the persistent tumor. A course of thio-tepa was equally unsuccessful. In November 1973 the patient entered

TABLE 1. *Effect of BCG on the rate of tumor recurrence*

Pt.*	Calendar of Cystoscopic Examinations				
	Pre-BCG			Post-BCG	
1	May 74	Aug. 74	Jan. 75	May 75	Aug. 75
	Pos.† (2)‡	Pos. (2)	Pos. (1)	Neg.§	Neg.
2	Jan. 73	June 73	Oct. 73	Jan. 74	Mar. 74
	Pos. (1)	Pos. (1)	Pos. (1)	Pos. (1)	Died
3	Sept. 73	Feb. 74	Sept. 74	Jan. 75	Apr. 75
	Pos. (2)	Pos. (1)	Pos. (2)	Neg.	Neg.
4	July 74	Sept. 74	Jan. 75	Apr. 75	June 75
	Pos. (1)	Pos. (1)	Pos. (1)	Neg.	Neg.
5	July 74	Nov. 74	Jan. 75	May 75	July 75
	Pos. (1)	Neg.	Pos. (4)	Neg.	Neg.
6	Sept. 73	Feb. 74	Aug. 74	June 75	Aug. 75
	Pos. (1)	Neg.	Pos. (3)	Neg.	Neg.
7	Feb. 73	June 73	Sept. 73	Nov. 74	May 75
	Pos. (3)	Pos. (2)	Pos. (1)	Neg.	Neg.

* Two patients with insufficient followup are omitted.
† Cystoscopy positive for tumor recurrence.
‡ Numbers in parentheses indicate number of recurrences in each examination.
§ Cystoscopy negative for tumor recurrence.

TABLE 2. *Summary of biopsy data*

Pt.	Post-BCG Biopsy
1	Not done
2	Marked inflammatory cell infiltrate, squamous cell carcinoma present
3	Granulomatous reaction and fibrosis with inflammatory infiltrate, no evidence of malignancy
4	Inflammatory reaction, epithelial dysplasia, no tumor present
5	Granulomatous reaction with multinucleated giant cells, infiltration with lymphocytes and plasma cells, no tumor
6	Focal granulomatous inflammation, giant cells and histiocytes about areas of necrosis, no tumor
7	Inflammatory infiltrate, focal areas of necrosis and calcification, no malignancy
8	Granulomatous inflammation, no tumor
9	Chronic inflammation, no evidence of malignancy