

Treatment of Carcinoma in situ of the Bladder with BCG

A Phase II Trial

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Summary. *Although carcinoma in situ conveys the idea of an early neoplasm, such lesions in the bladder mucosa commonly exhibit a very aggressive behavior and carry a grave prognosis. Seven patients with in situ carcinoma of the bladder have been treated with intravesical and systemic administration of Bacillus Calmette-Guérin. Elimination of tumor was documented by endoscopy, histology and cytology in five patients. These five patients have remained tumor-free for periods ranging between 12 and 33 months (mean: 22.6). This preliminary study indicates that regional and systemic immunotherapy is an alternative worth additional investigation in patients with carcinoma in situ of the bladder.*

Introduction

Pre-invasive or in situ carcinoma (CIS) of the urinary bladder was initially described by Melicow [7], but only after a considerable lapse were the peculiarities and significance of this neoplasm widely recognized [6]. From patients with CIS the clinician frequently elicits a history of bladder irritability and on endoscopy may find a normal-appearing urothelium or, more frequently, an irritated, 'velvety' bladder mucosa. A definitive diagnosis is made on the biopsy specimens, where the findings include an increase in the thickness of the urothelium and the nuclear-cytoplasmic ratio, hyperchromasia, lack of cellular maturation and loss of cellular polarity [2]. Characteristically, the lamina propria is not invaded although an inflammatory infiltrate may be present. Despite being a superficial lesion, CIS frequently becomes invasive and carries a grave prognosis. At present the recommended treatment for CIS is surgical, by means of radical cystectomy whenever possible.

We have previously found BCG of value in prevention of bladder tumor recurrence [8], and a study has shown that the vaccine is capable of inducing regression of papillary tumors of the bladder [3]. As an alternative to radical surgical treatment, the use of BCG in patients with CIS is being investigated. Preliminary results are presented in this report.

Patients and Methods

Seven patients with 'flat' CIS associated with one or more non-invasive papillary tumors were considered candidates for the trial because advanced age and/or medical reasons precluded an extensive open surgical procedure. Their ages ranged from 52 to 88 years (mean: 73.4 years). In every case the papillary tumors were fulgurated endoscopically but biopsies taken away from these lesions showed clear evidence of flat, pre-invasive carcinoma. The superficial nature of the tumor was established by bimanual examination and the biopsy specimens from suspicious areas of the mucosa, as well as biopsies from pre-selected sites of endoscopically healthy-appearing urothelium. Further details regarding the clinical presentation are shown in Table 1.

BCG (Intitute Armand Frappier, Montreal) was administered weekly, six times both by intravesical instillation (120 mg) and intradermally (5 mg) as previously described [8]. Eight weeks after the last immunization, cystoscopy and biopsies were obtained. Additional endoscopic follow-up has been continued at 3- to 6-month intervals for a minimum of 12 months. Urinary cytology of voided specimens has been done at regular intervals. The post-treatment observation period for this group of patients ranges from 12 to 33 months (mean 22.2).

Results

With one exception (case 6), all patients completed the treatment protocol and were available for follow-up. After three immunizations, case 6 had treatment interrupted due to a non-related illness;

Table 1. Form of presentation and results of BCG therapy in CIS of the urinary bladder

| Case | Age | Sex | Presentation | Follow-up ^a (months) |
|------|-----|-----|-------------------------------|---------------------------------|
| 1 | 69 | M | Hematuria, frequency, dysuria | Tumor-free [24] |
| 2 | 83 | F | Hematuria, urgency | Tumor-free [29] |
| 3 | 88 | M | Hematuria, clot retention | Tumor-free [33] |
| 4 | 52 | M | Hematuria, frequency | Tumor-present [24] |
| 5 | 78 | F | Urgency incontinence | Tumor-free [15] |
| 6 | 71 | M | Hematuria | Tumor-present [19] |
| 7 | 73 | M | Hematuria | Tumor-free [12] |

^a Results of follow-up as determined by biopsy and cytology of voided specimens

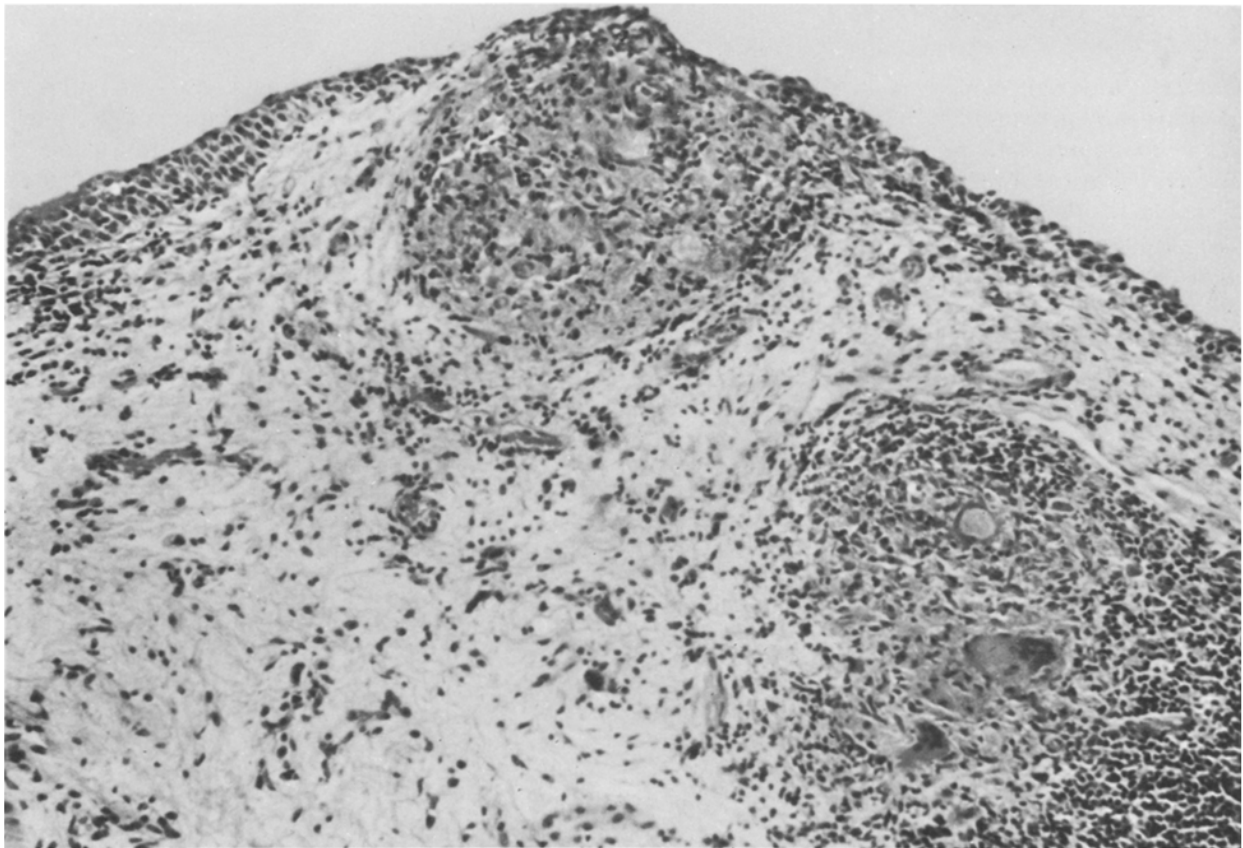


Fig. 1. Marked granulomatous inflammation following intravesical BCG administration. One of the granulomas is protruding through the mucosa, which is partially denuded

however, he is included in the overall evaluation of results.

Complications have been minimal and self-limiting. The commonly found cystitic symptoms after intravesical BCG are difficult to evaluate because they can be a manifestation of CIS. Bladder irritability prior to therapy was present in patients 1, 2, 4, and 5; it persisted during treatment but subsided spontaneously in patients 1, 2, and 4 between 2 and 4

weeks after completion of treatment. Patient 5 developed a bacterial infection, which responded rapidly to therapy and was followed by disappearance of her lower tract symptoms. After each immunization patient 2 complained of mild dysuria and urinary frequency which subsided spontaneously in 48–72 h. Low grade fever and malaise lasting for 2–3 days were reported by three patients (1, 2, and 5). In none of the patients were the symptoms severe enough to

interrupt or alter the schedule of immunizations. Anti-tuberculous therapy was not used.

The one patient not completing treatment (case 6) had a reactivation of a previously diagnosed reflux esophagitis requiring admission into the hospital. This was associated with psychogenic disturbances and refusal of additional treatment. Seven months after interruption of therapy a cystoscopy revealed no gross evidence of tumor but bladder biopsy demonstrated the presence of CIS.

Follow-up ranges from 12 to 33 months (mean: 22.2 months). Five patients (cases 1, 2, 3, 5, and 7) have remained tumor-free as determined by urinary cytology, endoscopy, and bladder biopsies.

Cystoscopy 8 weeks after completion of treatment showed variable degrees of inflammation in every patient. In only one patient (case 4) was the endoscopic appearance suggestive of carcinoma and this was confirmed histologically. The initial post-treatment biopsies invariably demonstrated a chronic inflammatory infiltrate frequently associated with granulomatous reaction (Fig. 1). Mild focal dysplasia was found in two patients (cases 1 and 2). The inflammatory changes observed histologically decreased progressively and became insignificant 6 months after completion of treatment.

Discussion

It is generally agreed that the natural history of untreated carcinoma in situ of bladder is toward invasion [1, 6, 11]. Pre-invasive carcinoma found in a limited area may be amenable to local treatment by wide fulguration or partial cystectomy [3, 4], but these limited forms of treatment are associated with a very high incidence of recurrent tumor [2]. Chemotherapy and radiotherapy appear to be of little value [6, 9, 12], although Farrow et al. [5] have recently shown thio-TEPA to be effective. Extensive CIS is best treated by radical cystectomy [10]. This approach, however, may be undesirable in the elderly and/or those patients in whom radical surgery carries unacceptable risks. The patients included in this study fell into these categories.

Superficial bladder tumors fulfill the requirements for successful BCG immunotherapy as defined by Zbar et al. [13]. Results obtained with BCG immunotherapy in this limited number of patients are gratifying and worth additional study. Not only was there evidence of tumor regression in the majority of patients, but they have remained tumor-free during a significant period of follow-up. These results support the findings of Douville et al. [3], who found

regression of papillary bladder tumors after BCG was administered in a form similar to ours. This regimen is sufficiently short to permit a prompt evaluation of results. Elimination of the tumor would avoid more aggressive therapy; if, however, tumor is still present after immunotherapy, conventional treatment modalities can be employed without significant detriment to the patient. In addition, the low morbidity associated with this regimen of BCG administration makes it particularly attractive. A higher incidence of undesirable effects related to systemic BCG infection following bladder instillation has been reported by Douville et al. [3], but they were readily controlled with specific anti-tuberculous medication.

The need for cold-punch biopsies in the follow-up must be emphasized. The endoscopic appearance is frequently deceptive, and more so in bladders harboring CIS. The cold-punch provides specimens of excellent quality allowing an accurate assessment of the urothelium, which is of paramount importance in the histological diagnosis of these lesions.

We [8] have previously reported the prophylactic value of BCG therapy in patients with a history of recurrent superficial tumors. The use of the vaccine in the treatment of existing lesions has been encouraging and warrants controlled phase III trials.

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