RESEARCH COMMUNICATION

Prevention of the Recurrence of Superficial Bladder Cancers: Intravesical Instillation of Bacillus Calmette-guerin Versus Bacillus Calmette-guerin Plus Epirubicin

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Abstract

Purpose The short-term effects of intravesical chemoimmunotherapy with epirubicin and Bacillus Calmette-Guerin (BCG) administered repeatedlly for prophylaxis of recurrence of superficial bladder cancer (pTa, pT1) were investigated in 22 patients with a median of 70 years between March, 1995 and February, 1999, and were compared with those of BCG monotherapy in 50 patients between March, 1995 and February, 1999.

Patients and Methods The patients underwent intravesical instillation of Tokyo-strain BCG with or without epirubicin after transurethral resection (TUR) of bladder cancer. For the combined treatment, at 1~2 weeks after TUR, epirubicin (40 mg) and BCG (80 mg) were instilled into the bladder by turn once a week for 12 weeks. For the BCG alone group, 80 mg instillation were performed with the same schedule. Thereafter, the patients were followed by cystoscopy and urinary cytology every 3 months for up to 3 years after intravesical therapy.

Results and Conclusions The simple recurrence rate was 22.7% (5/21) in patients with chemoimmunotherapy and 32.0% (16/50) in BCG-treated patients. Adverse reactions, including increased frequency of urination, urgency and miction pain, were observed in 18 patients (85.7%) undergoing chemoimmunotherapy and 58.0% undergoing BCG monotherapy. One patient receiving chemoimmunotherapy was withdrawn from treatment because of severe bladder-irritation symptoms due to instillation. Intravesical chemoimmunotherapy using epirubicin and BCG was inferior in comparison with BCG monotherapy for prophylaxis of recurrence of superficial bladder cancer.

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Key words: BCG, superficial bladder cancer, intravesical instillation, recurrence

Introduction

Approximately 80% of transitional cell carcinomas (TCC) present initially as superficial tumors confined to the mucosa and lamina propria. Transurethral resection (TUR) with cystoscopic and cytological follow-up is standard therapy for superficial bladder cancer. The major problems in the management of superficial bladder cancer are high recurrence rate and malignant progression after TUR (Richie, 1992; Shinka et al., 1989). Since multifocal field changes may contribute to recurrence of bladder tumors, additional treatment might be appropriate to supplement the endoscopic resection in certain patients. Indeed, intravesical chemotherapy and immunotherapy are now widely used to prevent or minimize the rate of recurrence after complete TUR of initial lesions in the bladder (Gamick et al., 1984; Glashan et al., 1990; Koontz et al., 1981; Lamm et al., 1985).

In 1976 Bacillus Calmette-Guerin (BCG) was used intravesically in patients with superficial bladder cancer for the first time. Since then, this therapeutic approach has become common and is now widely used for preventing the recurrence of superficial bladder cancers after transurethral resection of bladder tumors (TUR-Bt) as well as in therapy of carcinoma in situ (CIS) (Haaff et al., 1986; Catalona et al., 1987; Kavoussi et al., 1988; Sarosdy et al., 1989; Cookson et al., 1992). Direct anti-cancer effects for superficial bladder cancers have also been reported (Soloway et al., 1983), and BCG bladder instillation therapy has become the standard

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for both therapeutic and prophylactic control of superficial bladder cancers.

However, there are few studies regarding use of the combination of chemotherapy and immunotherapy for prophylaxis of recurrence after TUR. The present study was undertaken to evaluate the effects of chemoimmunotherapy with epirubicin and Bacillus Calmette-Guerin (BCG) for prophylaxis of recurrence after TUR.

Patients and Methods

Patient selection

A total number of 72 patients with superficial bladder cancer underwent treatment in Nagoya City University Medical School from March 1995 to January 1999. All patients had histologically documented transitional cell carcinoma at the beginning of the study. Patients with concomitant carcinoma in situ or bladder cancer with muscular invasion were excluded. Between March, 1995 and February, 1999 all patients received BCG monotherapy, and BCG and epirubicin combined immunochemotherapy was performed later. The maximum follow up period was three years, and the minimum period was 5 months in both groups. The characteristics of the patients are listed in Table 1. They were 63 men and 9 women from 33 to 85 years old. Of the 72 patients, 22 had grade 1 cancer, 47 grade 2 and the remaining 3 had grade 3 cancer . The pathological stage was pTa in 28 patients, pTl in 44.

Protocol design

Twenty-one patients underwent intravesical instillation of epirubicin (20~40 mg in 40 ml distilled water) 2 weeks after TUR of bladder tumors. The epirubicin was retained in the bladder for 1 h. One week after epirubicin instillation, Tokyo 172 strain BCG (80 mg in distilled water) was instilled into the bladder and retained for 2 h. Epirubicin and BCG were instilled into the bladder by turns once a week for 12 weeks. Fifty patients underwent BCG monotherapy once a week for 6 weeks and then once a month for 6 months. Thereafter, all cases were followed by cystoscopy and urinary cytology at 3 month intervals for up to 3 years after the end of intravesical instillation.

Evaluation of response

The response to chemoimmunotherapy was evaluated by cystoscopic examination with biopsy and cytology studies. For assessment of the efficacy of intravesical therapy, the findings were estimated by the simple recurrence rate, and by the cumulative nonrecurrence rate using the Kaplan-Meier method. For statistical comparisons, data were analyzed using the chi-square test, with findings at $p<0.05$ considered significant.

Results

Response

Five (22.7%) of 21 patients undergoing chemoimmunotherapy suffered recurrent tumors. Sixteen (32.0%) patients of the 50 patients treated with BCG alone suffered recurrent tumors. The mean time to recurrence in the combined therapy group was 23.8 months, while it was 7.1 months in the BCG monotherapy group. Chemoimmunotherapy was superior to BCG monotherapy for prophylaxis of recurrence after TUR until 2 years follow-up. However, comparison of Kaplan-Meier curves at the 3 year time point revealed significant lower tumor recurrence in the BCG monotherapy group at a level of p=0.026 (Fig.1).

Adverse reactions

Adverse reactions occurred in 18 (85.7%) of 21 undergoing combined therapy, compared with 29 (58.0%) of 50 receiving BCG monotherapy (Table 2). Local irritation symptoms were seen in 13 patients with combined therapy, usually beginning after 3 or 4 BCG instillations. Four of these exhibited systemic reactions, including flu-like symptoms and fever. When necessary, bladder irritation was controlled by antispasmodics and nonsteroidal anti-inflammatory drugs such as indomethacin. The severity of irritation symptoms also progressed as the frequency of instillations increased. Therefore, some patients received a decreased dose or prolonged interval of each instillation because of the severity of the symptoms. Only one patient undergoing combined therapy discontinued the treatment due to severe bladder irritation symptoms. No antituberculous agent such as isoniazid was administered to any patients with systemic reactions.

Discussion

The morbidity of repeated TUR for superficial bladder cancers is quite low. Close surveillance with endoscopic treatment of superficial lesions is appropriate for the majority of patients. However, 30-90% of patients have recurrent disease within 6 to 12 months if TUR is performed (Richie, 1992; Schoenberg et al., 1977).

The major problem in the management of superficial bladder cancer is the high rate of recurrence after endoscopic resection. This high rate of recurrence is due to many factors, including continuous exposure of the bladder epithelium to carcinogens, multifocal growth of the tumors, the implantation of tumor cells during TUR and incomplete tumor resection (Richie, 1992; Heney et al., 1978; Loening et al., 1980). For these reasons, intravesical chemotherapy and immunotherapy have been advocated for these patients at high risk for recurrence and progression (Gamick et al., 1984; Glashan et al., 1990; Koontz et al., 1981; Lamm et al., 1985; Soloway et al., 1981). The agents which have been most commonly used for bladder instillation are thiotepa,

mitomycin C, doxorubicin and BCG (Lamm et al., 1985). All have been effective in preventing tumor recurrence, and have achieved various increases in the rate of success in comparison with TUR alone (Gamick et al., 1984; Glashan et al., 1981; Lamm et al., 1985). The most effective of these appeared to be BCG. Immunotherapy with BCG has been used with success, because the response rates are ranging from 50 to 100% (Shinka et al., 1989; Lamm et al., 1985). Of the available measures, BCG treatment appears to offer the best promise. Many of the anti-cancer drugs which might alternatively be applied are in fact themselves carcinogenic (Lien et al., 1985). A second point which must be taken into consideration in this context is the strain of bacteria used. The Tokyo strain applied in the present study may give good protection against recurrence so that progression will not occur (Akaza et al., 1995, Akaza et al., 1989). This area clearly warrants further investigation. Another factor which should be investigated in future studies is the possible hazard of saline, shown to experimentally promote development of bladder lesions in rats after treatment with N-butyl-N-(4-hydroxybutyl) nitrosamine (Ohtani et al., 1984), and its replacement with distilled water. This latter medium has been shown to be a more effective vehicle for BCG against exfoliated bladder cells in vitro (Bolkier et al., 1995). However, other factors may operate in vivo, as suggested by the finding of improved attachment of BCG to bladder epithelium with saline administration (Hudson et al., 1989).

Since 1986, intravesical BCG immunotherapy has been used in our institute for prophylaxis after TUR of superficial bladder tumors, with a high success rate. However, posttreatment recurrence is common. In a previous study, we reported a case of inefficacy of BCG instillations (Okamura et al., 1996). Steinberg et al., (1991) reported that BCG or adriamycin alone had no effect on tumor growth. However, BCG plus adriamycin commenced weekly significantly inhibited tumor growth and progression in vivo in a rodent bladder cancer model. Uekado et al., (1994) reported that intravesical immunotherapy with epirubicin and BCG appeared effective as prophylaxis for recurrence in superficial bladder cancer since the recurrence rate was 3.5%. Therefore, since 1996, we have used epirubicin and BCG instillation in turn after TUR for superficial bladder cancer in an attempt to enhance the antitumor effect of BCG and reduce the rate of recurrence. Epirubicin has yielded superior therapeutic responses and a lower toxicity profile because it is more lipophilic than doxorubicin. Melekos et al., (1992) reported that 60%~63% of patients treated with epirubicin after TUR remained recurrence free (Melekos et al., 1993; Bedeir et al., 1997). Masters et al., (1999) suggested that the standard dose (1 mg/ml) was better in terms of marker tumor response or time to first recurrence.

However, in the present study, topical treatment of superficial bladder cancer with epirubicin and BCG proved to be non-effective for prophylaxis of recurrence. Thus, the simple recurrence rate after 3 years was 22.7%. Comparison of Kaplan-Meier curves for the time to recurrence revealed the delay in tumor recurrence in the monotherapy group to be significant (p=0.026). Although most patients tolerated the instillation schedule, the major problem with this modality appeared to be the high incidence of local adverse reactions. Therefore, we decreased the dose or prolonged the interval of each instillation in some patients. One patient had to be withdrawn from treatment due to symptoms of severe vesical irritation.

Recently, Witjes et al., (1998) reported that in a randomized prospective study of intravesical combined chemoimmunotherapy, mitomycin C and BCG were not effective compared with BCG monotherapy for superficial bladder cancer. The present findings should be considered as preliminary, since the observation period was relatively short. The present findings suggest that BCG monotherapy is more effective with less adverse reactions than intravesical chemoimmunotherapy using epirubicin or mitomycin C for prophylaxis of recurrence of superficial bladder cancer.

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