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Prospective Randomized Comparison of Intravesical BCG Therapy with Standard Dose Versus Low Doses in Superficial Bladder Cancer

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In this study, we evaluated low dose intravesical bacillus Calmette-Guerin (BCG) therapy following transurethral resection (TUR) in 80 patients with superficial bladder cancer. The patients were divided into two groups. Of the Connaught BCG strain 81 mg was given to 40 patients in Group 1 and 54 mg to the remainder of 40 patients in Group 2. BCG was introduced once a week for 6 weeks. Tumour recurrence was seen in 6 patients in Group 1 and in 10 patients in Group 2. Recurrence rates per month were 0.71 and 1.49, respectively. There was no significant difference in complication rates.

These data suggest that while the standard dose (81 mg) intravesical therapy of BCG is more effective than the low dose, there was no significant difference in side effects between the two groups.

Introduction

Seventy per cent of bladder tumours are superficial when they are first diagnosed [1, 2]. High recurrence of the tumour is important. Of the superficial bladder tumours 70% recur within the first year. Progression may occur in 3–5% of these patients [3, 4]. In a number of studies the efficiency of intravesical BCG treatment has been shown. To date the optimum dose of BCG is still controversial. In this prospective study, we compared the low and standard doses of intravesical BCG in the treatment of superficial bladder cancer.

Materials and methods

Eighty patients with superficial bladder cancer were treated with TUR followed by 6 weeks of intravesical BCG (IMMUNOCYT) therapy between 1990 and 1994.

For staging purposes all patients underwent cystoscopy. Selective site mucosal biopsies and resection of all visible tumours were performed. Preoperative excretory urograms were obtained to exclude upper tract disease.

The Connaught BCG strain (IMMUNOCYT) which contains 27 mg ($2.2–6.4 \times 10/12$ cfu) dye material was used. BCG instillations were begun as soon as irritative symptoms of TUR permitted. The patients were given 81 mg BCG weekly for 6 weeks in Group 1 and 54 mg in Group 2.

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All patients were followed up with urinary cytology and cystoscopic examination and random bladder biopsies. Tumour recurrence was defined as the evidence of papillary tumour. Progression was defined as the increase of stage or grade of the papillary tumour.

Monthly recurrence index was calculated as follows:

$$\frac{\text{Total recurrence number} \times 100}{\text{Total follow-up time (month) for all patients}}$$

Statistical significance was shown by Student's *t*-test.

Results

Of the 80 patients 63 were male and 17 were female. Mean age of patients was 55.3 years (32–70). The patients were randomized according to the factors affecting recurrences. Patient characteristics are shown in Table 1. There were no differences between the two groups in age, sex, grade, stage, size of tumour and previous recurrence rate.

Table 1
Patient characteristics of the two groups

	Group 1 (81 mg)	Group 2 (54 mg)
Age	55.27 (32–68)	56.28 (37–70)
Female	3	4
Male	22	21
Primary	19	17
Recurrent	6	8
Single	13	13
Multiple	12	12
Grade I	6	9
Grade II	14	13
Grade III	4	3
>3 cm	2	3
<3 cm	23	22
Ta	10	12
T1	15	13

After a mean 33.5-month follow-up period, 9 patients had recurrence (22.5%) and 1 had progression (2.5%) in Group 1. In Group 2, 16 had recurrence (40%), and 2 had progression with a mean 30-month follow-up. The follow-up time, recurrence and progression rates are shown in Table 2. Recurrence rates were 0.71 in Group 1 and 1.49 in Group 2. The difference in recurrence rates between the two groups is significant.

Table 2
Follow-up times and recurrence rates

	Group 1 (81 mg)	Group 2 (54 mg)
Number	25	25
Follow-up time	31.6 mo. (22–40)	26.8 mo. (19–38)
Recurrence	9 (22.5%)	16 (40%)
Recur. interval (average)	13.2 mo.	10.7 mo.
Recurrence (per month)	0.71	1.49
Progression	1.6 mo. (2.5%)	2 (5%)

There were no significant differences in side effects between the two groups (Table 3).

Table 3
Side effects of therapy

	Group 1 (81 mg)	Group 2 (54 mg)
Fever	4 10.0%	3 7.5%
Emesis	1 2.5%	1 2.5%
Flulike	12 30.0%	10 25.0%
Cystism	24 60.0%	19 47.5%
Haematuria	6 15.0%	14 35.0%
Urinary infection	2 5.0%	1 2.5%

Discussion

A large group of bladder tumours are stage Ta or T1. The aim of the treatment in superficial bladder cancer is resection of the tumour to prevent recurrence or progression. The recurrence rates were reported to be 40–70% in the first year [4]. In order to prevent recurrences many chemotherapeutic agents are used intravesically (Thiotepa, Adriamycin, Mitomycin, etc.). BCG immunotherapy was first applied by Morales [5]. Many reports claimed 42–88% success rate with TUR and intravesical BCG in the prevention of tumour recurrence [6, 7, 8]. In many of these studies BCG was found to be more effective than other agents. But still there is no optimal treatment protocol for BCG (Tice, Pasteur, Armond and Connaught). There are no differences in success rates between the strains used intravesically [9, 10].

Weekly intravesical BCG therapy is recommended for at least 6 weeks. But, because of cost and side effects, some authors suggested dosage lowering [11]. Lamm gave low dose (54 mg) Connaught strains of BCG to the patients. The response rate was 85% with a mean 18 months period. There are many reports comparing 6-week standard therapy with low dose therapy. On the other hand, in order to decrease recurrence and progression rates the low dose treatment is recommended to be longer than 6 weeks [11].

Cockett et al. found 59% success rate with low dose BCG therapy [13]. Pagano stated that low dose has 65% success rate [14].

In our study 80 patients with superficial bladder tumour were divided into two groups. Eighty-one mg BCG was given to 40 patients and 54 mg was given to the remainder for 6 weeks. The mean follow-up time was 33 months. Tumour recurred in 9 patients in Group 1 (22.5%) and in 16 patients in Group 2 (40%). Monthly recurrence index was 0.71 and 1.49, respectively. The difference between the two groups was significant.

It has been reported that low dose BCG has lower side effects than the standard dose [6, 12]. In our study group there were no significant differences. None of these patients discontinued BCG therapy due to side effects.

In conclusion, low dose BCG therapy has the same side effects as the standard dose, but the success rate is lower.

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