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A Randomised Prospective Study Comparing Intravesical Instillations of Mitomycin-C, BCG-Tice, and BCG-RIVM in pTa-pT1 Tumours and Primary Carcinoma *in situ* of the Urinary Bladder

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We compared intravesical instillations with mitomycin-C (MMC), Bacillus Calmette-Guerin (BCG) Tice, and BCG-RIVM in patients with pTa-pT1 papillary carcinoma and primary carcinoma *in situ* (CIS) of the bladder. Nine instillations with MMC were given or 6 weekly instillations with BCG. Early recurrences were treated with additional instillations. For toxicity and efficacy 437 patients were evaluated with a median follow-up of 32 months (range 12–56). Drug-induced and bacterial cystitis were the most frequent side-effects. The number and severity of side-effects (χ^2 test) were comparable in both BCG groups, but were significantly less in the MMC group for drug-induced cystitis ($P = 0.009$), other local side-effects ($P = 0.004$) and systemic side-effects ($P < 0.001$). The disease-free percentage (log-rank test) showed no significant difference for the three arms for papillary tumours ($P = 0.08$), nor the CIS ($P = 0.20$), although for CIS numbers are small. Additional instillations did not influence toxicity or efficacy.
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INTRODUCTION

IN PATIENTS with papillary superficial bladder cancer intravesical instillations have been used as prophylaxis to lower the high recurrence rate after complete transurethral resection (TUR) of a tumour. Both intravesical chemotherapy and intravesical immunotherapy have been used, and are superior to surgery alone in preventing tumour recurrence [1–3]. In patients with carcinoma *in situ* (CIS), complete TUR is difficult. In this case intravesical instillations are used 'therapeutically'. Intravesical chemotherapy in this study utilises mitomycin-C (MMC) because of its proven efficacy with regard to prevention of tumour recurrence and high response rate in patients with CIS [1, 4, 5]. Bacillus Calmette-Guerin (BCG) is the only immunotherapeutic drug that is widely used for superficial bladder cancer. BCG therapy induces an inflammation which consists of immune competent cells reflecting both a humoral and cellular response. However, the exact mechanism of action of BCG remains unknown. In several studies, with a median follow-up of between 12 and 48 months, 63–100% of the patients treated with intravesical BCG for papillary tumours remained disease free [6]. BCG is also effective for the treatment of CIS with complete response rates (negative cystoscopy, cytology and biopsies) of approximately 70% [5, 7–9].

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Few studies have compared chemotherapy and immunotherapy in a randomised setting [7, 10–13]. All studies show a higher efficacy of intravesical immunotherapy with BCG, although at the cost of more and more severe side-effects. However, differences in study design (e.g. total BCG dose) and patient selection (e.g. recurrent vs. non-recurrent patients) make it difficult to interpret these data. The first study comparing BCG-RIVM with MMC, showed no statistically significant differences in either toxicity or efficacy [10]. A possible explanation for this lack of difference was the relatively high number of pTaG1 tumours, known to have a low recurrence rate, masking a possible difference for the high risk groups. Also, the efficacy of BCG-RIVM was questioned. To compare the toxicity and efficacy of intravesical chemotherapy to intravesical immunotherapy, and to compare BCG-RIVM to a BCG strain with proven efficacy (BCG-Tice), we carried out a prospective multicentre study in patients with superficial bladder cancer.

PATIENTS AND METHODS

The objective of this randomised trial was to compare the toxicity and efficacy of intravesically administered MMC, BCG-Tice, and BCG-RIVM. From April 1987 until December 1990, 469 patients entered the study from 27 centres of the Dutch South East Cooperative Urological Group. All patients had histologically proven papillary pTa-pT1 transitional cell carcinoma of the bladder, with or without concomitant CIS, or primary CIS. In cases of papillary lesions a complete TUR was performed. Every area suspect for CIS was separately biopsied. In all cases selected biopsies of normal looking mucosa were taken to find concomitant abnormalities of the urothelium. Pretreatment studies included intravenous urogram, plain chest film, blood analysis, urine culture and cytology, and purified protein derivate (PPD) skin reaction. Exclusion criteria for the study were: any previous local or systemic cancer therapy or radiotherapy; any second malignancy, except basal cell or squamous cell carcinoma of the skin; untreated urinary tract infections, severe infections or active or cured tuberculosis; blood urea or creatinine raised more than twice above the upper limit for the local laboratory; expected difficulties in the follow-up period of at least 5 years. After approval of the medical ethical committee and provision of written informed consent, patients were randomised to one of the three treatment arms.

All specimens of tumour and bladder biopsies were reviewed by a single pathologist for stage and grade. Pathological classification was according to the TNM system [14], grading of the tumours according to Koss [15]. The maximal stage and grade of all tumour specimens reviewed were used to characterise each patient. Patients presenting with papillary tumours and (concomitant) CIS were classified according to the highest tumour stage, which was CIS, and subsequently analysed according to the response to CIS.

Treatment

Intravesical instillations were started between 7 and 15 days after complete TUR in the case of a papillary lesion, or after biopsy in the case of CIS. Patients with CIS were treated with a regimen similar to that for patients with papillary tumours. After instillation the patient was instructed to refrain from voiding for at least 1 h.

Intravesical chemotherapy was undertaken with 30 mg MMC 'Kyowa' (Cristiaens), diluted in 50 ml normal saline. MMC was given once a week for 4 weeks, and thereafter once a month for the next 5 months. In the event of a recurrent superficial tumour or persistent CIS at 3 months the treatment schedule was not changed after a complete TUR (or biopsy). In the event of a superficial recurrence or persistent CIS after 6 months, 3 additional monthly MMC instillations were given.

For intravesical immunotherapy BCG-Tice (Organon Teknika) or BCG-RIVM (the Dutch BCG strain, Lundbeck) was used. The BCG dose was 5×10^8 bacilli in a solution of 50 ml of normal saline. BCG was given once a week for 6 consecutive weeks. At the time of the first superficial recurrence or persistent CIS at 3 or 6 months, a second 6-week course with BCG instillations was given after complete TUR or biopsy. In all other cases of recurrences, irrespective of the treatment arm, the patient left the study and treatment was at the discretion of the urologist.

Side-effects were divided in local, allergic and systemic side-effects. Local toxicity was defined as the occurrence of culture-proven bacterial cystitis (not BCG related), drug-induced cystitis (MMC or BCG related) or other local side-effects, such as haematuria, prostatitis and epididymitis. The severity of side-effects was classified into three categories: requiring no delay, delay, or cessation of instillation therapy. Side-effects were scored by using a symptom score, physical examination and blood and urine studies, during instillations and every 3 months thereafter. In BCG-treated patients PPD skin reaction was monitored. In all patients control cystoscopy studies were performed every 3 months during the first 2 years of the study, every 4 months in the third and fourth year, and every 6 months thereafter. In cases of a first recurrent tumour at or after 9 months of study, in cases of recurrences both at 3 and 6 months, and in cases of recurrent tumour with increase of pT category to pT2 or higher, the patient left the study. Progression was defined as an increase in pT category, or the development of CIS after a pTa or pT1 papillary tumour. A higher tumour grade (upgrading) was not considered progression. With papillary tumours the response was measured by the duration of the disease-free interval (negative cystoscopy and cytology). With CIS, complete response was defined as negative cystoscopy, negative cytology, and negative biopsies. Partial response was not defined and not used as an objective in this study. Follow-up data are analysed yearly.

Statistical considerations

In order to detect a difference of 50% in the median duration of the disease-free interval between MMC and the best (smallest hazard rate) of the BCG treatments (assuming the time to recurrence follows an exponential distribution), 90 eligible and evaluable patients followed until recurrence were required in each treatment arm (error probabilities $\alpha = 0.05$ and $\beta = 0.20$). Assuming that 65% of the patients will have at least one recurrence during the course of the study, 138 evaluable patients per treatment arm were needed, a total of 414 evaluable patients. Block randomisation (blocksize 6 = 3 treatments × 2 patients/treatment) was used. Estimation of the cumulative distribution of the disease-free interval was performed by the method of Kaplan–Meier for each of the three treatment groups and for subgroups. Differences in the distribution of the disease-free interval were tested with the log-rank test. For testing of the difference between sample percentages the χ^2 test was used. All statistical computations were made using SAS (statistical analysis system).

RESULTS

Of the 469 patients who entered the study, 156 patients were allocated to the MMC group, 154 to the BCG-Tice group, and

Table 1. Patients' characteristics and allocation to treatment

	MMC	BCG-Tice	BCG-RIVM	Total
No. patients	156	154	159	469
Excluded	8	14	10	32(6.8%)
Evaluated	148	140	149	437
Mean age (years)	65.5	65.9	66.0	65.8
Male/female	119/29	121/19	129/20	369/68

159 to the BCG-RIVM group. 17 patients (3.6%) were ineligible because of the following reasons: no malignancy after pathological review ($n = 9$), > pT1 after pathological review ($n = 6$) and prior intravesical chemotherapy ($n = 2$). Another 15 patients (3.2%) were excluded from subsequent analysis for different reasons. Analysis included the remaining 437 patients, with a median follow-up after randomisation of 32 months (range 12–56). Patient characteristics such as age and sex ratio, and tumour stage and grade were equally distributed between the three treatment arms (Tables 1 and 2). Of the 50 patients with CIS, 25 had pure flat multifocal CIS and 25 also had papillary tumours (concomitant CIS). Allocation to treatment arm of the evaluable patients is shown in Table 2. A total of 197 patients (68 × MMC, 60 × Tice, 69 × RIVM) left the study because of the following reasons: first recurrence at or after 9 months (89), protocol violation (34), progression in tumour stage to pT2 or higher (23), side-effects (14), intercurrent death (10), further treatment refusal (7), lost to follow-up (2), other (18).

Side-effects

The number and severity of side-effects were comparable in patients with papillary tumours and CIS, therefore these groups were not separated. All side-effects which were encountered during the instillation period (6 months for MMC, 6 weeks for BCG) are listed in Table 3. Between the BCG groups there was no statistical difference in number and severity of the side-effects. Drug-induced cystitis, other local side-effects and systemic side-effects were significantly more frequent in the BCG groups. A more detailed analysis of the systemic side-effects is shown in Table 4. Intravesical instillations were delayed only 35 times (10.0% of all side-effects) but in 11 patients (3.1% of all side-effects, 2.5% of all patients) treatment had to be stopped due to the side-effect. No haematological toxicity, such as myelosuppression in MMC-treated patients, was noted. Additional MMC instillations ($n = 4$) or a second course of BCG (25 × Tice, 24 × RIVM) did not influence the number and severity of side-effects. No treatment-related deaths were recorded.

Table 2. Tumour characteristics of evaluated patients at entry and allocation to treatment

	MMC	BCG-Tice	BCG-RIVM	Total
G1	24	28	32	84
pTaG2	55	48	54	157
G3	4	5	4	13
				254 (65.6%)
G1	—	—	—	—
pT1G2	31	18	23	72
G3	22	18	21	61
				133(30.4%)
Primary	104	87	108	299
Recurrent	32	30	26	88
Total papillary tumours	136	117	134	387
CIS	12	23	15	50
Total	148	140	149	437

Efficacy of treatment

In the group of 50 patients with CIS the complete response rate in the MMC group was 42% (5/12), in the Tice group 70% (16/23), and in the RIVM group 47% (7/15). These results were not significantly different ($P = 0.20$), but numbers are small. Of all CIS patients 28 had a complete response (56%).

In total, 134 of 387 patients with papillary tumours (34.6%) experienced a recurrence during the follow-up period. The disease-free percentage in each treatment arm after 1 and 2 years is shown in Table 5. No statistically significant difference is observed in the Kaplan–Meier plots (disease-free percentage) between the three treatment arms (Fig. 1, $P = 0.08$). In patients with grade 3 tumours the efficacy of MMC was borderline significantly higher compared with BCG-treated patients ($P = 0.05$). Additional MMC instillations or a second course of BCG in patients with papillary tumours did not influence treatment efficacy. Progression in stage to pT2 or higher was observed in 8 (5.4%) patients of the MMC group, in 7 (5.0%) patients of the BCG-Tice group, and in 8 (5.4%) patients of the BCG-RIVM group.

DISCUSSION

This is the first randomised study in which efficacy and adverse effects of intravesical instillations with a chemotherapeutic agent and two different BCG strains have been compared. In most reports intravesical BCG has been found to be more toxic than intravesical chemotherapy for superficial bladder cancer [8]. Severe systemic complications and even fatal sepsis have been described. The first reports also indicated a high percentage (up to 90%) of BCG-induced cystitis and other local and systemic side-effects [16, 17]. However, more recent reports, including the present study, indicate that BCG-induced cystitis is observed less frequently [11]. This can be explained by the fact that severity of local and systemic side-effects may be judged differently by different investigators. Some urologists will stop instillations in the presence of more or less severe drug-induced cystitis or fever, while others believe that BCG only works if at least irritative symptoms appear and they will not consider these as side-effects [18]. Consensus should be reached upon how to define local and systemic toxicity in BCG therapy and how to treat it [11]. Severe local and systemic side-effects, apart from one case of BCG pneumonitis, were not observed in the present study. There was no difference with regard to adverse effects between the two investigated BCG strains. However, BCG induced more side-effects than MMC, both locally and systemically. The exception is culture proven bacterial cystitis (not BCG induced). This varies between 18% and 27% in the different groups, indicating that intravesical instillation itself may induce urinary tract infection in a considerable number of patients.

Efficacy results should be interpreted with caution because we have not yet reached the median duration of the disease free interval in either of the three treatment arms after a median follow-up of 32 months. Comparing a 6 week BCG schedule to 6 months MMC therapy, however, this interim analysis does not provide evidence that BCG offers a better response in the

Table 3. Side-effects during instillation period

	MMC	BCG-Tice	BCG-RIVM	Total
Total patients	148	140	149	437
Bacterial cystitis ($P = 0.20$)				
Without delay	25	26	24	75
With delay	1	11	10	22
Stop treatment	1	1	—	2
Total	27 = 18.2%	38 = 27.1%	34 = 22.8%	99 = 22.7%
Drug-induced cystitis ($P = 0.009$)				
Without delay	25	40	45	110
With delay	1	1	2	4
Stop treatment	–	1	1	2
Total	26 = 17.6%	42 = 30.0%	48 = 32.2%	116 = 26.5%
Allergic reaction ($P = 0.30$)				
Without delay	4	2	2	8
With delay	1	1	1	3
Stop treatment	2	—	—	2
Total	7 = 4.7%	3 = 2.1%	3 = 2.0%	13 = 3.0%
Other local side-effects* ($P = 0.004$)				
Without delay	7	23	20	50
With delay	—	—	2	2
Total	7 = 4.7%	23 = 16.4%	22 = 14.8%	52 = 11.9%
Systemic side-effects ($P < 0.001$)				
Without delay	6	32	24	62
With delay	—	3	1	4
Stop treatment	—	3	2	5
Total	6 = 4.1%	38 = 27.1%	27 = 18.1%	71 = 16.2%

* Haematuria, prostatitis and epididymitis. Testing of the difference between sample percentages with the χ^2 test.

treatment of CIS than MMC ($P = 0.20$), although the numbers are small. In the prevention of recurrences after complete TUR of papillary tumours BCG is also not superior to MMC ($P = 0.08$). The efficacy of MMC in grade 3 tumours is even borderline significantly higher ($P = 0.05$). The results in the present study confirm those of a previous reported trial in which BCG-RIVM was compared with MMC [10]. Could this difference with other studies have been caused by patient selection? In this study 84 patients with pTaG1 tumours have been treated. Patients with low stage, low grade tumours have a low risk for recurrence or progression if the tumour is solitary and primary. However, the recurrence rate increases from 0.17 to 0.32 if patients present with multiple primary pTaG1 tumours, or even to 0.61 if a patient has multiple recurrent pTaG1 tumours [19]. Only 39 (8.9%) had solitary primary pTaG1 tumours. This indicates that 91.1% of the patients may have had at least potential benefit of adjuvant intravesical therapy after TUR.

Although intravesical chemotherapy delays the time to first recurrence, it probably does not influence progression and survival [20]. For BCG therapy this seems to be different,

Table 4. Detailed analysis of systemic side-effects

	MMC	BCG-Tice	BCG-RIVM	Total
Fever < 38.5°C	—	7	4	11
Fever > 38.5°C	—	2	1	3
Flu-like symptoms	1	11	4	16
Nausea	—	2	1	3
General malaise	2	10	5	17
Skin symptoms	1	—	—	1
Arthralgia	—	1	1	2
Pneumonia	—	—	1	1
Sepsis	—	1	—	1
Other	2	4	10	16
Total	6	38	27	71

Table 5. Treatment efficacy

	MMC	BCG-Tice	BCG-RIVM
Percentage disease-free with standard error, all papillary tumours			
	$n = 136$	$n = 117$	$n = 134$
1 year	76% ± 4%	68% ± 4%	69% ± 4%
2 years	65% ± 5%	54% ± 5%	62% ± 5%
Percentage disease free with standard error, grade 3 papillary tumours			
	$n = 26$	$n = 23$	$n = 25$
1 year	79% ± 8%	55% ± 11%	64% ± 10%
2 years	(*)	46% ± 13%	50% ± 12%

* No failure yet after 2 years.

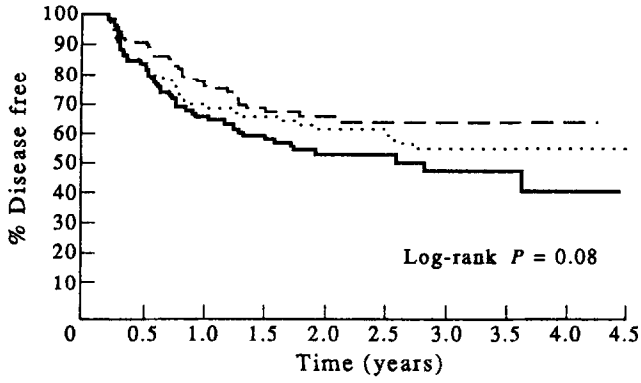

Fig. 1. Kaplan–Meier plots of the percentage of patients with papillary tumours pTa and pT1, grade 1–3 transitional cell cancer, free of tumour after TUR and treatment with MMC (dashed line), BCG-Tice (solid line) and BCG-RIVM (dotted line). Log-rank test: $P = 0.08$.

especially when maintenance BCG is used. In the case of maintenance therapy additional BCG instillations are given after the initial 6-week course, for example monthly and/or 3-monthly instillations during 1 or 2 years. Several recent studies suggested that maintenance BCG alters prognosis and improves survival instead of simply delaying recurrences [21–23]. During maintenance BCG therapy, however, side-effects can be more pronounced than during one or two 6-week courses. This underlines the importance of the toxicity of BCG. The question remains for which selected patients maintenance BCG is indicated, because it is obvious that a 6-week course is suboptimal for some patients.

In conclusion, the results of this prospective randomised multicentre study show that overall toxicity of intravesical instillations is acceptable. MMC produces significantly less side-effects. There is no difference in side-effects nor efficacy between BCG-Tice and BCG-RIVM. Also, this study confirms the earlier study that intravesical instillation with MMC (4 weekly instillations, followed by 5 monthly instillations) is as effective as BCG-RIVM (one or two courses of six intravesical instillations) with regard to the recurrence rate in patients with pTa/pT1 papillary tumours [10]. The absence of an advantage for BCG in CIS patients might be explained by small numbers of patients in these groups.

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