CLINICAL RESEARCH

Effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: interim report from the Medical Research Council Subgroup on Superficial Bladder Cancer (Urological Cancer Working Party)

D A TOLLEY, T B HARGREAVE, P H SMITH, J L WILLIAMS, K M GRIGOR, M K B PARMAR, L S FREEDMAN, B M USCINSKA

Abstract

A randomised control trial of intravesical instillation of mitomycin C was conducted in 457 patients with cancer of the bladder that was confined to the submucosa on histological examination. The events studied were the recurrence free rate, the recurrence rate/year, and the number of new tumours developing/year. At the initial cystoscopy the tumours were completely resected and the patients randomised to have no instillation of mitomycin C, a single instillation of 40 mg in 40 ml of water at that cystoscopy, or a single instillation and then four further instillations. All patients had follow up cystoscopies every three months for the first year, twice in the second year, and yearly thereafter. After a median of 12 months, follow up information was available for 397 patients.

Patients receiving both the single instillation of mitomycin C

and the instillations at five cystoscopic examinations had significantly lower yearly recurrence rates and tumour rates than those in the control group, and the group receiving multiple instillations fared significantly better than those receiving a single instillation. The figures on progression to invasive cancer were too small to allow conclusions to be drawn.

Introduction

Malignant tumours of the bladder comprise about 3% of all malignancies, and most are in histological categories Ta and T1.¹ Though many of the tumours are easy to treat,^{2,3} recurrences occur after complete resection of the tumour in up to 70% of patients^{4,5} and a large proportion of these recurrences are of a higher grade of malignancy than the primary tumour.⁶ In 10% of cases the tumours progress to invasive carcinoma.^{4,5} The mortality from carcinoma is from 4% to 12% after five years,^{7,8} and the overall survival rate three years after transurethral resection is about 72%.⁹

Jones and Swinney¹⁰ were the first to suggest that intravesical chemotherapy might reduce the rate of recurrence of superficial bladder tumours. Since then many intravesical agents have been used both as primary treatment and as adjuvant treatment after complete transurethral resection to try to prevent the development of subsequent tumours.

Attendance for frequent instillation is a nuisance for the patient as well as being costly for both patient and hospital. The Medical Research Council Subgroup for Superficial Bladder Cancer has previously reported a randomised study of adjuvant intravesical thiotepa.¹⁰ That study investigated two simple schedules of instillation: either a single dose at the time of resection of a newly diagnosed cancer, or repeated doses at the next four cystoscopic examinations, which were performed three monthly. Patients in the control group received no chemotherapy. Initial analysis of the data showed no beneficial effect from chemotherapy. We now report a randomised study of the effect of mitomycin C given by a similar regimen.

Royal Infirmary, Edinburgh

D A TOLLEY, FRCS, consultant urologist

Western General Hospital, Edinburgh

T B HARGREAVE, MB, BS, consultant urologist

St James's University Hospital, Leeds

P H SMITH, MB, FRCS, consultant urologist

Royal Hallamshire Hospital, Sheffield

J L WILLIAMS, FRCS, consultant urologist

Department of Pathology, University of Edinburgh

K M GRIGOR, BSC, MD, senior lecturer

MRC Cancer Trials Office, 5 Shaftesbury Road, Cambridge CB2 2BW

M K B PARMAR, MSc, DPhil, statistician

L S FREEDMAN, MA, DIP STAT, statistician

B M USCINSKA, MSc, data manager

Correspondence to: Mr Tolley.

Patients and methods

A total of 502 patients with newly diagnosed Ta or T1 transitional cell carcinoma of the bladder were entered into the study from 17 participating centres between March 1984 and December 1986 (table I). The patients were required to be free of urinary infection, to have an adequate degree of performance (0-2 on the World Health Organisation scale), a white cell count of more than $3 \times 10^9/l$ and a platelet count of more than $100 \times 10^9/l$. After complete transurethral resection of the tumour patients were randomly allocated to receive no instillations of mitomycin C (control group), a single instillation of 40 mg mitomycin C in 40 ml water immediately after the transurethral resection (group 1), or an instillation of 40 mg mitomycin C in 40 ml water immediately after the transurethral resection and, additional instillations at the four check cystoscopies performed during the first year (five instillations in all).

TABLE I—Total number of patients entered from each hospital

Hospital	Clinicians	No of patients entered
Princess Royal Hospital, Hull	DW Newling	34
Western General Hospital, Edinburgh	TB Hargreave	47
	JE Newsam	
	GD Chisholm	
Morrison Hospital, Swansea	KW Vaughton	27
	MB Rose	
St James's University Hospital, Leeds	PH Smith	67
	P Whelan	
Royal Hallamshire Hospital, Sheffield	JI Williams	51
Royal Infirmary, Edinburgh	DA Tolley	44
York District Hospital, York	B Richards	17
Clayton Hospital, Wakefield	R Adib	30
Castleford, Normanton and District Hospital, Castleford	M Robinson	24
Freeman Hospital, Newcastle	RR Hall	35
Churchill Hospital, Oxford	GJ Fellows	33
Airedale General Hospital, Keighley	I Appleyard	12
Derby Royal Infirmary, Derby	KW Munson	28
The London Hospital, London	JP Blandy	4
Royal Infirmary, Glasgow	D Kirk	18
New Cross Hospital, Wolverhampton	L Beynon	19
Wordsley Hospital, Stourbridge	M Rowse	12

TABLE II—Reasons for exclusion of 45 patients

Reason for exclusion	No of patients
Previous carcinoma	1
Other tumour outside bladder	1
No histological evidence of tumour	1
Tumour not transitional cell carcinoma	4
Tumour too far advanced	38
Total	45

All histological examinations were done by the same reference pathologist.

Check cystoscopies were to be done every three months for the first year, twice during the second year, and yearly thereafter. At each cystoscopy any tumour or abnormal looking urothelium was resected and tissue sent to the reference pathologist to confirm recurrence. Side effects were noted.

Forty five patients were excluded (table II), most because unexpected muscle invasion was found on histological examination, leaving 457 patients for analysis (table III). The groups were well matched.

The aim was to enter a total of 400 patients into the trial. Assuming that the data for about 80% of these patients would be evaluable, we had a 90% chance of detecting a difference of 20% in recurrence free rates at two years. Randomisation (from sealed envelopes) was carried out in the operating theatre immediately after the operation to allow instillation, if allocated, to be carried out at once. The trials office monitored the randomisation to ensure firstly that envelopes were not opened out of sequence and, secondly, that all randomised patients were registered with the office.

Recurrence free rates were calculated by the actuarial method and compared by the logrank test.¹¹ The recurrence rate/year in each treatment group was estimated by the formula: number of cystoscopies at which tumour is found/length of follow up (years), where both numerator and denominator are totalled over all patients in the group. The tumour rate/year was estimated similarly by the formula: number of tumours seen at follow up cystoscopies/length of follow up (years). Pairwise comparisons (control group v group 1, control group v group 2, and group 1 v group 2) of the recurrence rates and tumour rates were made using a permutation test¹²; this

TABLE III—Details of patients and tumours at time of entry to trial

	Control group (n = 158)	Group 1 (n = 152)	Group 2 (n = 147)	Total No (%) (n = 457)
Age (years):				
24-50	14	19	13	46 10.1
51-60	48	37	35	120 26.3
61-70	50	56	53	159 34.8
71-80	41	34	43	118 25.8
81-100	5	6	3	14 3.1
Length of history (months):				
0-6	128	115	119	362 79.2
7-12	17	24	17	58 12.7
13-24	11	8	5	24 5.3
25-100	2	5	5	12 2.6
Unknown	0	0	1	1 0.2
No of tumours:				
1	112	120	103	335 73.3
2	21	13	24	58 12.7
≥3	25	19	19	63 13.8
Unknown	0	0	1	1 0.2
Histological category of tumour:				
pTX	2	2	1	5 1.1
pTa	84	70	72	226 49.5
pT1*	66	68	66	200 43.8
Unknown	6	12	8	26 5.7
Histological grade of tumour:				
GX	0	2	0	2 0.4
G1	65	50	48	163 35.7
G2	74	73	76	223 48.8
G3	13	15	15	43 9.4
Unknown	6	12	8	26 5.7

*This category included 20 T1 tumours invading superficial strands of smooth muscle in submucosa but not superficial detrusor muscle.

is a non-parametric test that makes no assumption about the distribution of numbers of recurrences or tumours/patient within each group.

Results

Information about follow up was available for 397 patients: 130, 129, and 138 in the control group and groups 1 and 2, respectively; the median follow up was 12 months. Side effects were not a severe problem. Ten patients had dysuria or frequency; nine were in group 2 and one in group 1. Seven patients had cystoscopic evidence of delayed healing at the site of resection of the tumour, six in group 2 and one in group 1. This condition was seen more than once in a few patients. These patients were free of symptoms and the persistent defect eventually healed. Histological examination of biopsy specimens confirmed that all tumour had been removed in each case.

We studied the effect of mitomycin C on superficial recurrence in terms of the recurrence free rate, the recurrence rate, and the tumour rate, in agreement with recent international consensus.¹² The recurrence free rate uses information only about the time to first recurrence, and the recurrence rate uses information about subsequent recurrences as well thus providing a longer term measure of the effect of treatment. It is calculated as the number of cystoscopies/year at which cancer is found. The tumour rate is the rate at which new superficial tumours develop and is similarly expressed as the number of new tumours/year.

Of the 397 patients for whom follow up information was available, 186

Recurrence free times for control group, group 1 (one instillation of mitomycin C), and group 2 (five instillations of mitomycin C).

(47%) developed at least one recurrence. The recurrence free rates are shown in the figure and at two years were 35%, 39%, and 58% for the control group, group 1, and group 2, respectively. The difference between group 1 and the control group is small and not significant (ratio of risks of recurrence = 1.13, 95% confidence interval (CI) 0.79 to 1.6, logrank $\chi^2 = 0.46$ with 1 df, $p = 0.5$). There was, however, a large difference between group 2 and the control group (ratio of risk of recurrence = 1.62, 95% CI 1.11 to 2.35, logrank $\chi^2 = 6.3$ with 1 df, $p = 0.01$). At the time of the first cystoscopy there was little difference between the recurrence free rates (75% for the control group, 72% for group 1, and 78% for group 2). The recurrence rates for the three groups and the results of the permutation tests for pairwise differences in the recurrence rates are shown in table IV. These data show that all patients who received mitomycin C (group 1 and group 2) experienced lower rates of recurrence than those who did not receive mitomycin C. Furthermore, the comparison between group 1 and group 2 shows a considerably lower recurrence rate for patients who received five instillations. Table V shows the tumour rates for the three groups. These were qualitatively similar to the recurrence rates and similar conclusions may be drawn.

Eight patients subsequently developed invasive (pT2) tumours; three were in group 2, three in group 1, and two in the control group. Five patients were withdrawn from the study because of the development of multiple recurrences that required alternative treatment; three were in the control group, and two in group 1. Longer follow up and larger numbers of patients are required before the effect of mitomycin C on these two endpoints may be adequately assessed.

TABLE IV—Pairwise comparisons* of recurrence rates among control group (recurrence rate/year 1.0), group 1 (recurrence rate/year 0.67), and group 2 (recurrence rate/year 0.43)

	Control group v group 1	Control group v group 2	Group 1 v group 2
Ratio of recurrence rates	1.5	2.3	1.5
95% Confidence interval	1.1 to 2.0	1.7 to 3.4	1.1 to 2.3
p Value	0.02	<0.0005	0.03

*Permutation procedure.

TABLE V—Pairwise comparisons* of tumour rates among control group (tumour rate/year 3.7), group 1 (tumour rate/year 1.5), and group 2 (tumour rate/year 0.8)

	Control group v group 1	Control group v group 2	Group 1 v group 2
Ratio of tumour rates	2.5	4.6	1.8
95% Confidence interval	1.5 to 4.7	2.7 to 7.3	1.0 to 3.2
p Value	0.001	<0.0005	0.06

*Permutation procedure.

Discussion

Many regimens of intravesical chemotherapy have been tried in attempts to reduce the recurrence rates of superficial bladder cancer. These generally require frequent attendance for instillation.^{13,14} Mitomycin C has been shown to be active in treating superficial bladder cancer, and when given in multiple instillations it is clearly effective, producing response rates of 40% to 50%.¹⁴ Nakazone and Kinoshita¹⁵ reported that the recurrence rate after multiple post-operative instillations of mitomycin C was less than after a similar regimen of thiotepa after three years, and was significantly lower than in patients receiving no intravesical treatment. The value of mitomycin C as an adjuvant treatment has also been suggested in a non-randomised study.¹⁶ Multiple instillations of mitomycin C, however, are associated with an increased incidence of side effects.¹⁷ For this reason and in view of the cost incurred by frequent hospital attendance, single instillation at the time of cystoscopy would be preferable if shown to be effective.

The results of this study show that the instillation of 40 mg mitomycin C at the time of resection of the tumour reduces the subsequent recurrence rate. In addition, if 40 mg mitomycin C is instilled at each subsequent cystoscopy for the first year, the recurrence rate is further reduced, and the time before the first recurrence is lengthened. Comparing the control group and group 2, we estimate that the number of recurrences is roughly halved

(0.43) by giving five instillations of mitomycin C during the first year.

The benefit of intravesical instillations in lowering recurrence rates must be balanced against toxicity. The incidence of side effects in this study was extremely low, although delayed healing at the resection site was seen in some cases. The presence of benign symptomless ulcers at the resection site after instillation of mitomycin C is of some importance, because the endoscopic appearances may be mistaken for persistent infiltrating bladder cancer. Biopsy of persistent lesions after instillation of mitomycin C is mandatory if unnecessary aggressive treatment is to be avoided.¹⁸ The reduction in recurrences achieved by single instillations of mitomycin C is encouraging, though the result was established over only a relatively short period (median follow up 12 months). If this benefit is maintained for a longer period, cystoscopy schedules could be relaxed with a consequent saving of inconvenience and cost to both patient and clinician.

The potential benefit of reducing the number of superficial recurrences may also reduce the proportion of patients developing invasive bladder tumours (pT2), or multiple superficial recurrences that are difficult to control endoscopically. Because both these events occur comparatively rarely among patients with newly diagnosed superficial tumours, large numbers of patients need to be followed for several years to detect such an effect. It is therefore unlikely that this study alone will furnish such evidence, though the question may be answered by combining data from several studies of intravesical chemotherapy.

We conclude that instillation of 40 mg mitomycin C in 40 ml water at the time of transurethral resection and at each subsequent cystoscopy for one year results in reduced recurrence rates and an increase in the recurrence free time.

Members of the MRC subgroup on superficial bladder cancer (urological working party) are: D A Tolley (chairman), L L Beynon, G J Fellows, L S Freedman (statistician), K M Grigor, R R Hall, T B Hargrave, K Munson, D W W Newling, B Richards, M R G Robinson, M B Rose, P H Smith, J L Williams, P Whelan.

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