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Adjuvant Intravesical Mitoxantrone After Transurethral Resection of Primary Superficial Transitional Cell Carcinoma of the Bladder. A Prospective Randomised Study

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A prospective randomised controlled clinical trial began in 1989 on 126 patients with superficial transitional cell carcinoma of the bladder (pTa–pT1, grades 1–3) to compare the efficacy of adjuvant topical mitoxantrone after transurethral resection versus no further treatment. 62 patients received no further treatment, 64 patients received weekly 20 mg mitoxantrone intravesically for 6 weeks after differentiated TUR of all visible tumours. The endpoint of the study was any progression of stage or grade or further recurrences. The median follow up was 29 months—the minimum follow up was 24 months. The percentage of recurrences (25.8 versus 23.4), the recurrence rate (1.2 versus 0.9), the overall disease free interval and the tumour progression rate showed no statistically significant differences ($P > 0.05$ Mantel-Cox test). Only the comparison of time to recurrence in tumours with recurrences showed a statistically significant difference, with a longer disease free interval for the TUR plus mitoxantrone group ($P = 0.016$ Mantel-Cox test).

Key words: superficial bladder cancer, recurrence prophylaxis, mitoxantrone, randomised trial
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INTRODUCTION

SUPERFICIAL TRANSITIONAL cell carcinoma (STCC) are classified into stages pTa to pT1 and grades 1 to 3 according to the recommendation of the International Union Against Cancer and the World Health Organization [1, 2]. After complete resection of all visible lesions, STCC will recur, the majority within 12 month after the initial transurethral resection (TUR) in approximately 50–60% ranging from 36 to 82% according to the literature of phase III studies with a TUR group alone and according to the different risk groups [3]. The tumour progression rate after TUR alone is between 7 and 20% [4–8]. The aim of this study was to examine the efficacy of a new cytotoxic drug to prevent recurrences and progression.

MATERIAL AND METHODS

130 patients entered the study of which the data of 126 were available, 4 patients being excluded because of missing follow up data.

After the evaluation of a STCC by differentiated TUR, the patients were randomised according to RAN-code, ADV, Munich into TUR alone and TUR plus weekly instillations of 20 mg mitoxantrone. Study information and written consent were obtained. Mitoxantrone, a synthetic anthracendion with a molecular weight of 517.4, was instilled for 6 weeks beginning 6–10 days after the initial TUR. Patients with concomittant carcinoma *in situ* (TIS) were excluded from the study. The follow up was with endoscope every 3 months for the whole observation period. Cytological examinations were not performed routinely. The evaluation was performed after the last patient reached the minimum follow up of 24 months. The median follow up was 29 months.

Statistical analyses

For statistic analysis the BMDP Statistical Software (Berkeley, California, U.S.A.) was used. The recurrence free interval is defined as the time from the primary TUR to the first recurrence. The curves to the time of first recurrence were evaluated according to the method of Kaplan-Meier [9].

RESULTS

There was a balanced distribution of sex, age, tumour stage and tumour grade in both groups. (Table 1; $P > 0.1$). The distribution of other risk factors, including multiplicity, tumour size, dysplasia in the mapping, localisation of the tumour and absence of tumour-associated inflammatory reaction, was also well balanced ($P > 0.1$, Table 2).

Recurrences

The percentage of recurrences after TUR alone was 25.8 versus 23.4% in the group with mitoxantrone. The recurrence rate was 1.2 versus 0.9 and the recurrence free interval 9.7 months versus 13.1 months. The Kaplan-Meier curves show no statistical significant difference (Figure 1; Table 3). It is of interest that the comparison of recurrent tumours shows a

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Table 1. *Frequencies of sex, age, tumour stage and tumour grade in* 126 *patients with primary superficial transitional cell carcinoma of the bladder*

Therapy	*n*	Male (%)	Mean age (years) ± SD	Stage (%) pTa	pT1	Grade (%) 1	2	3
TUR alone	62	67.7	67.2 ± 10.7	71.0	29.0	64.5	35.5	–
TUR + mitoxantrone	64	71.9	69.8 ± 9.5	70.3	29.7	60.9	37.5	1.6

TUR, transurethral resection; SD, standard deviation.
Comparison of frequencies were based on Pearson chi square test or Yates-corrected chi square test and showed a P value of >0.1.

Table 2. *Frequencies of multiplicity, tumour-weight, dysplasia in bladder mapping, localisation of tumour and presence of tumour associated tissue inflammatory reaction (TATIR) in* 126 *patients with primary superficial transitional cell carcinoma of the bladder*

Therapy	% Solitary	% Tumour weight <5g	Mapping % D1–2	% Localisation of tumour Base	Back	Side	Dome	% TATIR present
TUR alone	79.0	80.6	6.5	51.5	16.1	25.9	6.5	17.7
TUR + mitoxantrone	76.6	82.8	12.5	37.5	21.9	37.5	3.1	6.3

TUR, transurethral resection; SD, standard deviation; D1–2, dysplasia grades 1–2.
Comparison of frequencies were based on Pearson chi square test or Yates-corrected chi-square test and showed a P value of >0.1.

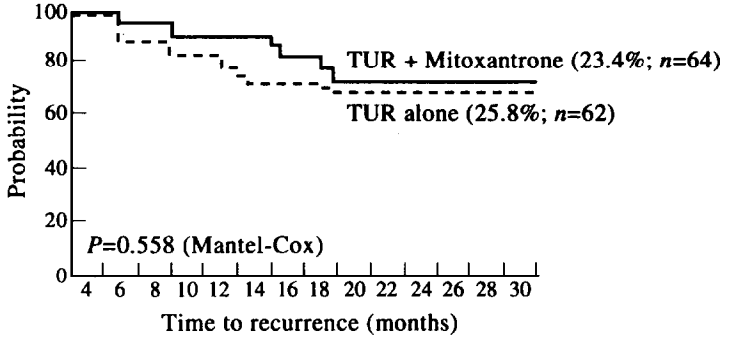

Figure 1.

Table 3. *Frequencies of mean follow-up, recurrences, recurrence rate and mean recurrence free interval in* 126 *patients with primary recurrent transitional cell carcinoma of the bladder*

Therapy	Mean follow-up ± SD	% Recurrences	Recurrence rate	Mean recurrence free interval ± SD
TUR alone	28.6 ± 6.2	25.8	1.2	9.6 ± 3.6
TUR + mitoxantrone	29.4 ± 6.4	23.4	0.9	13.1 ± 4.8

TUR, transurethral resection; SD, standard deviation.
Comparison of frequencies were based on Pearson chi square test or Yates-corrected chi square test and showed a P value of >0.1. The comparison of recurrence rate was based on the Mann-Whitney U test ($P>0.1$). The comparison of mean interval free of recurrence was based on the Wilcoxon test ($P>0.1$).

Table 4. Frequencies of persisting tumours, tumour progression, recurrences with down-staging and down-grading, number of recurrences and multiplicity of recurrences in 126 patients with primary superficial transitional cell carcinoma of the bladder

Therapy	% of persisting tumours	% Tumour-progression		% Recurrences with down-staging /-grading	% Number of recurrences		% Multilocal recurrences
		Overall	Muscle invasive		1	2	
TUR alone	6.5	6.5	–	4.8	21.0	5.0	12.9
TUR + mitoxantrone	3.1	7.1	0.8	3.1	20.3	3.1	7.8

TUR, transurethral resection; SD, standard deviation.
Comparison of frequencies were based on Pearson chi square test or Yates-corrected chi square test and showed a P value of >0.1.

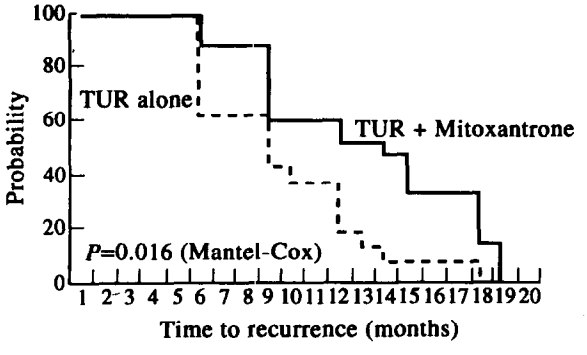

Figure 2.

statistically significant prolonged time to recurrence after TUR plus mitoxantrone versus TUR alone (Figure 2).

The percentage of persisting tumours, tumour progression, down-staging or down-grading in the recurrent tumour, the number of recurrences and the tendency to multilocal recurrences were comparable in both groups, and showed no statistical difference ($P > 0.1$; Table 4).

Tumour progression

One patient (0.8%) with a primary pTa grade 2 tumour and negative bladder mapping had a recurrence after 9 months (solitary pTa grade 2), and 6 months later a muscle invasive progression. All other tumour progressions were in stage or grade within the determination of STCC.

Side effects

In 7 patients (11%) of the mitoxantrone group, a chemocystitis was observed, but in no case was toxicity so severe that the treatment had to be stopped.

DISCUSSION

The main problem in recurrence prophylaxis of STCC is the completeness of the initial TUR. Up to 25% residual tumour can be found, if an adequate second look TUR is routinely performed [4, 10–13]. In our study, we tried to solve this problem performing a differentiated and if necessary repeated TUR with special examination of the tumour margin [14].

Reports of phase I–II studies using mitoxantrone are rare. Stewart and colleagues proved, in a phase I study in patients with recurrent STCC after prior intravesical therapy, that 10 of 22 patients had a longer recurrence free interval after therapy with mitoxantrone [15].

Sharifi and associates evaluated side effects in 23 patients with STCC and adjuvant mitoxantrone and found a good tolerability with 10.5 mg per instillation, and bladder irritations with a dosage between 12 and 13.5 mg per instillation [16]. We could not confirm these results in our study with 20 mg per instillation, and we believe that 20 mg is an adequate dosage of an antracycline cytostatic drug.

The Italian group of Serratta and colleagues reported a reduction of recurrences per year from 1.6 to 0.78, in a group of 36 patients with primary and recurrent STCC, after treatment by mitoxantrone at a dosage of 20 mg per instillation without severe side effects [17]. Özcan and colleagues report on different intracavitary dosages (10 versus 20 mg) of mitoxantrone. The follow up was short (5–7 months) with 2.3% recurrences after the lower dose and no recurrences after the higher dose of mitoxantrone [18]. Is, in primary STCC, an additive treatment with side effects of approximately 10% and a severe progression expectation of approximately 1% necessary? Our results do not support this, because 75% had no further recurrences and only 1% had a severe progression. What we can achieve in this group of patients is an increased prolonged time to the first recurrence.

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A Comparison of Polychemotherapy and Melphalan/Prednisone for Primary Remission Induction, and Interferon-alpha for Maintenance Treatment, in Multiple Myeloma. A Prospective Trial of the German Myeloma Treatment Group*

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406 untreated multiple myeloma patients of stage I (n = 54), II (n = 148) and III (n = 204) were enrolled in the trial. 51/54 stage I and 60/148 stage II patients were asymptomatic and followed without treatment until disease progression (progression free survival: 60% after 4 years for stage I versus 50% after 1 year for stage II). Symptomatic patients of stage I (n = 3/54) and II (n = 88/148) presenting with tumour progression, received melphalan 15 mg/m^2 intravenously (i.v.) and prednisone 60 mg/m^2 oral days 1–4 (MP). Stage II disease remission rate was 59%, and 50% tumour related survival (TRS) was 59 months. Stage III patients were randomised to receive MP or VBAMDex (vincristine/BCNU/doxorubicin/melphalan/dexamethasone) treatment. 43% of MP treated patients responded compared with 64% of the VBAMDex group. 50% TRS was 36 months in both groups without a detectable difference. 117 responders of stage II and III with stable disease were randomised to receive either IFN-α (5 × 10^6 IU, subcutaneous (S.C.) 3 times per week) or no maintenance treatment. The relapse rate in both groups was 50% after 13 months. No survival benefit for IFNα treated patients was observed (50% TRS: 45 months).