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Single-dose versus multiple instillations of epirubicin as prophylaxis for recurrence after transurethral resection of pTa and pT1 transitional-cell bladder tumours: a prospective, randomized controlled study

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Objective To compare single-dose and multiple instillations of epirubicin in the chemoprophylaxis of superficial bladder tumours.

Patients and methods In a prospective randomized and controlled study, 168 evaluable patients were assigned to three groups after transurethral resection of bladder tumour (TURBT) and histological confirmation of its superficial nature (pTa and pT1). The groups were comparable for tumour stage, grade and other tumour characteristics. In group 1, patients received a single dose of 50 mg epirubicin in 50 mL normal saline immediately after TURBT; group 2 received 50 mg epirubicin in 50 mL normal saline 1–2 weeks after TURBT and the instillations were repeated for 8 weeks and thereafter monthly to complete one year of treatment; group 3 (control group) received no adjuvant therapy after TURBT. The patients were assessed by cysto-urethroscopy, urine cytology and DNA flow cytometry 8 weeks after resection and then every 3 months during the first 2 years and 6 monthly thereafter during the next 2 years. Intravenous urography was performed annually and when otherwise indicated.

Results The recurrence rate was significantly lower in the patients treated with epirubicin than in the control group (24, 25 and 52%, respectively; $P<0.001$). In those receiving epirubicin, the rates of recurrence were statistically comparable ($P=0.9$). Patients who had a large tumour burden showed slightly lower recurrence rates with single-dose epirubicin than with delayed maintenance therapy but the difference was statistically insignificant. Patients with a history of bladder tumours before treatment had lower recurrence rates with maintenance treatment than with a single dose (34.6 and 22.6% in groups 1 and 2, respectively); again this difference was statistically insignificant. Patients with grade 3 tumours showed a marginal difference in favour of maintenance therapy. The rates of progression amongst the three groups were 5.5, 3.4 and 9.3%, respectively, with no significant differences. The overall toxicity rates were comparable in the two treated groups (22 and 25%).

Conclusion With the possible exception of grade 3 tumours, single-dose immediate epirubicin is as effective as delayed maintenance therapy, with the advantage of being more cost-effective.

Keywords Bladder tumours, intravesical therapy, epirubicin, single-dose, maintenance

Introduction

Epirubicin (4′-epi-doxorubicin) has proved as effective but less toxic than its parent compound doxorubicin [1,2]. A single instillation of this relatively new drug has been reported to be therapeutically effective in 46% of patients [3]. A single intravesical instillation of some drugs, e.g. thiotepa and doxorubicin, immediately after TURBT of papillary bladder TCC (stages pTa and pT1) significantly reduced the rate of tumour recurrence when compared with placebo treatment [4,5].

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However, the need for a properly conducted prospective randomized and controlled study comparing a single instillation of epirubicin and more intensive treatment prompted the present study.

Patients and methods

This prospective randomized controlled study conducted between January 1992 and February 1996 included 181 patients. All underwent a complete transurethral resection of visible tumours and stage pTa and pT1 TCC of the bladder was confirmed histologically in all but two patients, in whom the tumour was proved to be muscle-invasive.

Patients were included if tumours fulfilled one or more of the following criteria: grade 2 or 3, multiple, recurrent, stage pT1 on definitive pathology, an aneuploid pattern of DNA on flow cytometry and large ($\geqslant 3$ cm in the greatest dimension). Patients with pTa tumours were included in the study if they had multiple, large, recurrent and/or grade 2–3 tumours. Patients were included if they had adequate cardiac, haematological, renal and bladder functions and had not received prior chemotherapy or pelvic irradiation.

Pre-operatively, all patients were evaluated by serum creatinine measurement, urine analysis, urine culture, a full blood count, plain X-ray (UTP), an IVU, chest X-ray and ECG. If a urinary tract infection was diagnosed it was treated until the urine became sterile.

Treatment schedule

Under spinal anaesthesia, patients were examined bimanually and then by cysto-urethroscopy, when bladder-wash specimens for DNA and cytology were taken and all visible papillary tumours were completely resected using electrodiathermy. Thereafter, multiple cold-cup random biopsies were taken from areas nearby and away from the tumour site(s) including the prostatic urethra. After adequate haemostasis, a two-way 20-F Foley catheter was inserted. Then according to the randomization schedule adopted, patients were randomly allocated to one of three groups. Patients in group 1 received a single dose of 50 mg epirubicin in 50 mL normal saline immediately after insertion of the catheter, and the catheter clamped for 2 h. Patients in group 2 received eight weekly epirubicin instillations of the same dose, concentration and duration as for group 1, starting 1–2 weeks after resection, and followed by 10 monthly doses to complete one year of treatment. Patients in group 3 (control group) received no adjuvant treatment after TURBT.

The cystoscopic and pathological characteristics of the tumours were recorded; these characteristics were comparable in the three groups (Table 1). Eleven patients were further excluded from the study because they were diagnosed as having associated carcinoma *in situ* in the random biopsies obtained from their bladders. In group 1, five patients were excluded because the pathology was adverse, i.e. one with muscle-invasive disease and four with carcinoma *in situ*. Therefore, the study included 168 evaluable patients (49 women and 119 men, mean age 55.7 years, range 30–72).

The duration of follow-up ranged from 16 to 49 months (mean 32.2, SD 11.4). The post-resection follow-up included cysto-urethroscopy, cytology and DNA flow cytometry 8 weeks after resection and then every 3 months during the first 2 years, and 6-monthly thereafter

Table 1 Tumour characteristics in the three groups

No. (%)	*Group 1*	*Group 2*	*Group 3*	P*
No. of patients	55	59	54	
Stage				
pT_a	9 (16)	15 (25)	10 (19)	0.4
pT_1	46 (84)	44 (75)	44 (81)	
Grade				
G_1	6 (10)	11 (19)	14 (26)	
G_2	30 (55)	33 (56)	29 (54)	0.2
G3	19 (35)	15 (25)	11 (20)	
DNA ploidy				
Diploid	41 (75)	47 (80)	42 (78)	
Tetraploid	8 (15)	10 (17)	7 (13)	0.6
Aneuploid	6 (10)	2 (3)	5 (9)	
Multiplicity				
Single tumour	34 (62)	33 (56)	35 (65)	0.6
Multiple	21 (38)	26 (44)	19 (35)	
Size <3 cm	36 (66)	42 (71)	34 (63)	0.6
$\geqslant 3$cm	19 (34)	17 (29)	20 (37)	
History of recurrence				
De novo	29 (53)	28 (48)	31 (57)	0.5
Recurrent	26 (47)	31 (52)	24 (43)	
Mean age (range)	52.1 (36–65)	55 (30–68)	53.4 (32–72)	
Sex				
Male	37	44	38	
Female	18	15	16	

*Chi-squared test.

during the next 2 years. All patients underwent an annual IVU unless otherwise indicated. Urine analysis, urine culture, a full blood count and ECG were requested before each instillation and any abnormality was treated accordingly.

Statistical analysis

The recurrence rates, interval to first tumour recurrence and progression rates during the study period were compared among the three groups, and between the first two groups collectively and the control group. The recurrence rate was defined as the number of patients with recurrence during the follow-up period divided by the total number of patients in the same group(s), multiplied by 100. The mean interval to first recurrence was defined as the interval between the last resection and first cystoscopic study positive for recurrence. The observed differences were considered statistically significant if the P for differences by chance alone was <0.05.

Recurrence with or without progression was considered the end-point of the study. In the presence of positive cytology and/or an aneuploid DNA pattern on flow cytometry during follow-up in the absence of cystoscopically visible tumours, multiple random biopsies were taken, including the tumour resection site(s) and prostatic urethra to exclude neoplastic recurrence in the bladder.

Results

The recurrence rates in the three groups were 24, 25 and 52%, respectively ($P<0.002$; Table 2). Calculated as the recurrence rate per 100 patient-months, i.e. the number of recurrences diagnosed cystoscopically in every group during the study period divided by the total months of follow-up and multiplied by 100, were 0.79, 0.84 and 2.01, respectively, for the three groups. The recurrence rate for the first two groups collectively was 24.5% and this rate was significantly lower than the rate in the control group (52%) ($P<0.001$; Table 2). There was no significant difference between the first two groups in recurrence rate ($P=0.8$) or the mean interval to first tumour recurrence ($P>0.05$; Table 2). The interval to first tumour recurrence was significantly longer in the groups 1 and 2 than in the control group ($P<0.05$, Table 2).

The recurrence pattern was related to different tumour characteristics (Table 3). In patients who had a large tumour burden (multiple *de novo* tumours and/or tumours $\geqslant 3$ cm in the greatest dimension) the differences in recurrence were not statistically significant between groups 1 and 2 ($P=0.4$ and 0.5, respectively; Table 3). Patients who had developed rapid recurrences before treatment had lower recurrence rates with maintenance treatment than with single-dose epirubicin but again, the difference was insignificant statistically ($P=0.5$; Table 3). Patients with grade 3 tumours in group 2 showed lower recurrence rates than those in group 1 ($P=0.05$; Table 3). Groups 1 and 2 were statistically

Table 3 Incidence of recurrence in groups 1 and 2 in relation to different tumour variables

	Group 1	*Group 2*	
	Number/total in category		P*
Multiple tumours	5/21	10/26	0.4
Large tumours	4/19	7/17	0.5
Recurrent tumours	9/26	7/31	0.5
Stage			
pTa	0/9	0/15	0.7
pT1	13/46	15/44	
Grade			
G1	0/6	3/11	–
G2	3/30	9/33	0.3
G3	10/19	3/15	0.05
DNA status			
Diploid	8/41	12/47	0.6
Tetraploid	2/8	2/10	0.7
Aneuploid	3/6	1/2	0.4

*Chi-squared test.

Table 2 Recurrence and progression rates in the three groups

No/total (%)	*Group 1*	*Group 2*	*Group 3*	P
Recurrence rate	13 (24)	15 (25)	28 (52)	0.002*
Chemotherapy versus control	28/114 (25)		28/54(52)	<0.001†
Recurrence rate in groups 1 and 2	13/55 (24)	15/59 (25)	–	0.8†
Mean interval to tumour recurrence (months)	16	18	6.9	<0.05†
Progression rate	3 (5.5)	2 (3.4)	5 (9.3)	0.4*

*Chi-squared test. †Student's *t*-test.

comparable in the rates of recurrence for all other tumour variables ($P > 0.05$; Table 3) and the three groups had statistically comparable progression rates (5.5, 3.4 and 9.3%, respectively).

Toxicity and side-effects of the drug were noticed in 22 and 25% of the patients in groups 1 and 2, respectively (no significant difference, $P = 0.8$; Table 4). No patient in either group developed systemic toxicity. Side-effects were mostly in the form of irritative bladder symptoms, i.e. dysuria, urgency and frequency. Severe toxicity occurred in eight patients (three in group 1 and five in group 2). Among the former patients, two had significant haematuria and one had urinary tract infection, and in the latter, three had haematuria, one a urinary tract infection and the fifth a contracted bladder. Patients in both groups who developed haematuria were treated conservatively and the haematuria improved after 2–5 days. Patients with urinary tract infections were given appropriate antibiotics and urine samples taken 2 days after therapy for culture; all these samples were confirmed as sterile. Intravesical epirubicin instillation was discontinued for 1–2 weeks in four of the five patients with severe toxicity in group 2 and this discontinuation was permanent in the patient with a contracted bladder.

Discussion

In 1977, Farrow *et al.* [6] suggested that there are probably two origins for TCC of the urothelium, i.e. a primary lesion that will progress into an invasive tumour if not modified by treatment, and the field-change theory, which proposes that the lesion is surrounded by CIS and possibly other dysplastic mucosal changes that give rise to subsequent tumours [6]. In both instances, tumour cell implantation at the time of TURBT could be prevented by concomitant adjuvant instillation of intravesical chemotherapy and this proposal was supported by other studies [4,7,8]. Doxorubicin has been shown in several studies to be locally and systemically absorbed, with cardiotoxicity being the main systemic side-effect [9,10].

Epirubicin is characterized by the rarity of toxic systemic effects because of its minimal trans-urothelial absorption; the local side-effects may be the same in type and frequency as those reported for adriamycin [11]. Thus, epirubicin was the chemotherapeutic agent preferred for immediate post-resection prophylaxis in the present study.

The comparable efficacy of both immediate single-dose epirubicin and delayed maintenance treatment in the present study supports the impression that tumour cell implantation may be at least partly responsible for the high incidence of recurrence of bladder tumours and supports the beneficial role of chemotherapeutic agents given at the time of resection in reducing this incidence [4,5,8]. Also, the comparable efficacy of both regimens strengthens the theory that further adjuvant therapy may have no significant effect on prophylaxis for recurrence of superficial bladder tumours [4,5,12]. In the present study, the incidence of recurrence was related to several variables of which tumour stage, grade, DNA ploidy status, multiplicity, history of bladder tumour and size of the tumour are the most important, and the results were in accordance with the work of others [13]. Patients with multiple and/or large tumours showed a marginal difference in favour of single-dose immediate epirubicin, possibly because after the resection of such tumours, a large area of traumatized urothelium would be created that would have provided a fertile area for tumour cell implantation unless the latter process was modified by concomitant adjuvant intravesical therapy. The minimal role for single-dose epirubicin in grade 3 tumours is in accordance with the results of Zincke *et al.* [5] and supports the need for adjuvant and more aggressive treatment in such tumours. A similar but statistically insignificant advantage for maintenance therapy over the single-dose regimen was noted in patients with a history of bladder tumours. However, the surprising observation of the negligible effect of additional interval treatments needs to be examined further in studies over longer periods of follow-up.

Side-effects and toxicity rates were slightly lower than those reported previously and there was no additional hazard related to the instillation of epirubicin in the period immediately after TURBT [11,14].

In conclusion, with the possible exception of grade 3 tumours, single-dose epirubicin is as effective as multiple-interval treatment, with a similar rate of toxic and untoward side-effects and with the advantage of better cost-effectiveness. There were no statistically significant differences in progression among the three groups, but over a longer period of follow-up, intravesical chemotherapy may prove more effective for this aspect.

Table 4 Toxic effects in the groups 1 and 2 (epirubicin)

No (%)	*Group 1*	*Group 2*	P*
Overall toxicity	12 (22)	15 (25)	0.8
Mild toxicity	9 (16)	10 (17)	0.8
Severe toxicity			
Haematuria	2	3	
UTI	1	1	
Contracted bladder	–	1	
Total	3 (5.5)	5 (8.5)	0.7

*Chi-squared test.

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