0022-5347/97/1581-0068$03.00/0
THE JOURNAL OF UROLOGY
Vol. 158, 68–74, July 1997
Printed in U.S.A.

INTRAVESICAL EPIRUBICIN VERSUS DOXORUBICIN FOR SUPERFICIAL BLADDER TUMORS (STAGES pTa AND pT1): A RANDOMIZED PROSPECTIVE STUDY

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ABSTRACT

Purpose: We performed a prospective, randomized, controlled study to compare intravesical epirubicin and doxorubicin as adjuvant therapy after endoscopic resection of superficial bladder tumor.

Materials and Methods: We randomly allocated 253 eligible patients to 4 study arms. Seven to 14 days after transurethral bladder tumor resection instillation of the intravesical agent was instituted, including 50 and 80 mg. epirubicin in study arms 1 and 2, respectively, and 50 mg. doxorubicin in arm 3. Control arm 4 included patients who underwent transurethral bladder tumor resection alone. Instillation was repeated weekly for 8 weeks and monthly thereafter to complete 1 year of treatment. All patients were followed every 3 months by cystourethroscopy, urine cytology and deoxyribonucleic acid flow cytometry for 12 to 48 months (mean 30.1).

Results: Rates of recurrence were significantly lower in the chemotherapy groups than in controls ($p < 0.001$) and in the epirubicin groups than in the doxorubicin group ($p = 0.02$). In arms 1 to 4 recurrence rates were 25, 17.6, 36.7 and 65.6%, respectively. Recurrence rates per 100 patient months were 0.83, 0.60, 1.18 and 2.73, respectively, which were significant statistically, and lower after chemotherapy in general and epirubicin in particular ($p < 0.05$). Mean interval to first recurrence was 16, 15.4, 18.9 and 6.3 months, respectively, with a significant difference between the chemotherapy and control groups ($p < 0.05$). Progression to muscle invasive disease occurred in 7 (10.9%), 3 (4.4%), 6 (10%) and 5 patients (8.2%), respectively, in arms 1 to 4 ($p > 0.05$). We studied the relationships among different risk factors, and patterns of recurrence and progression. For pT1 tumors recurrence rates in arms 1 to 4 were 26.3, 17.8, 39.3 and 70.9%, respectively, which were significantly lower in the chemotherapy group than in controls ($p < 0.001$) and in the epirubicin groups than in the doxorubicin group ($p = 0.01$). Toxic and untoward side effects developed in 10 (15.6%), 16 (23.5%) and 25 (41.7%) patients in chemotherapy arms 1 to 3, respectively, with a marginal insignificant difference between low and high dose epirubicin ($p = 0.3$), and significantly lower toxicity rates in arms 1 and 2 than in 3 ($p = 0.002$). A contracted bladder developed in 2.1% of all patients who received chemotherapy.

Conclusions: This study demonstrates that epirubicin has better efficacy and lower toxicity than doxorubicin when used as an intravesical agent.

KEY WORDS: bladder; bladder neoplasms; doxorubicin; epirubicin; carcinoma, transitional cell

Superficial bladder tumors comprise 75 to 85% of all bladder cancer in Europe and the United States,[1] and approximately 20 to 30% of bladder cancers in Egypt.[2] Although the primary modality of treatment of stages Ta and T1 disease, and carcinoma in situ is transurethral bladder tumor resection, surgery does not prevent recurrence or progression to muscle invasive disease. However, 50 to 70% of patients have recurrent disease within 6 to 12 months if transurethral bladder tumor resection alone is done.[3]

The potential benefit of intravesical therapy is to prevent or decrease tumor recurrence and possible progression to muscle invasive disease.[4] Among the effective intravesical agents used for the treatment of stages pTa and pT1 tumors the anthracycline, doxorubicin, and its derivative, epirubicin, have been shown to be effective therapeutically and prophylactically.[5,6] The incidence of recurrence after transurethral bladder tumor resection and adjuvant doxorubicin has been described as 30 to 38%.[4,7] Epirubicin (4'-epidoxorubicin) has been introduced to effect the same therapeutic response and a lower toxicity profile than the parent compound doxorubicin.[8] Epirubicin has been used in different doses ranging from 30 to 100 mg. per dose with the most suitable dose being 50 mg.[9,10]

Accepted for publication December 6, 1996.
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PATIENTS AND METHODS

Between June 1991 and May 1995 we performed a prospective randomized controlled study of 253 eligible patients, including 206 men and 47 women who underwent transurethral bladder tumor resection. Postoperative histopathological evaluation confirmed the nature of the tumors (stages Ta and T1 transitional cell carcinoma). The efficacy and side effects of epirubicin in 2 concentrations and doxorubicin for prophylaxis of the recurrence of superficial bladder tumors (stages pT1 and pTa) were compared.

Study eligibility criteria included high grade and/or stage pT1 disease, rapid recurrence within 6 months of initial

resection, multicentricity, aneuploid deoxyribonucleic acid (DNA) pattern, size equal to or more than 3 cm. in the greatest dimension, associated carcinoma in situ or other dysplastic mucosal changes, positive posterior urethral biopsy and/or positive postoperative urinary cytology. There was no prior pelvic radiotherapy or chemotherapy, and cardiac, hematological, renal and bladder function was normal. Only 2 patients in whom a posterior urethral biopsy was positive were enrolled in this study and they underwent resection of multiple tumors encircling the bladder neck to provide bladder neck incompetence and sufficient contact of drugs with the prostatic urethra.

All patients were evaluated at the start of the study and at each followup. Initial evaluation included baseline laboratory investigations, urinalysis, urine culture, serum creatinine, complete blood count, urinary tract plain x-ray, excretory urography, bladder wash for cytology and DNA studies, bimanual examination using anesthesia and histological diagnosis after transurethral bladder tumor resection. Evaluation at each visit included urinalysis, urine culture, serum creatinine, complete blood count, electrocardiography and urine pH before and after each instillation. Cystourethroscopy, urine cytology and flow cytometry were performed every 3 months during the first 2 years and 6 months thereafter, and excretory urography was done yearly.

Patients were randomly allocated to 4 study arms that were comparable regarding tumor stage, grade, DNA pattern and other criteria (table 1). Patients in arm 1 received 50 mg. epirubicin diluted in 50 ml. normal saline that were retained intravesically for 2 hours per instillation, whereas those in arms 2 and 3 received 80 mg. epirubicin in 50 ml. normal saline and 50 mg. doxorubicin in 50 ml. normal saline, respectively. Patients in control arm 4 did not receive any adjuvant treatment. Instillation was initiated 7 to 14 days after transurethral bladder tumor resection and repeated weekly for 8 weeks, and then monthly to complete 1 year of treatment. Followup ranged from 12 to 48 months (mean 30.1).

Intervals to first recurrence and progression were shown as Kaplan-Meier survivorship curves and results were compared globally among the 4 groups. Paired comparisons between different arms were made using the log rank test. Differences in the recurrence rate and recurrence rate per 100 or 12 patient months were compared using a nonparametric permutation test with $p < 0.05$ considered significant. Recurrence rate was defined as the number of patients with recurrence in each arm as a percent of the total number during followup. Recurrence rate per 100 or 12 patient months was defined as the total number of positive cystoscopic studies irrespective of the number of tumors divided by total months of followup from the date of the last transurethral bladder tumor resection at study entry until the final cystoscopic examination, multiplied by 100 or 12.

TABLE 1. *Tumor characteristics in the 4 study arms*

	No. Arm 1	No. Arm 2	No. Arm 3	No. Arm 4	Total No. (%)
Stage:					
pT1	57	56	56	55	224 (88.6)
pTa	7	12	4	6	29 (11.4)
Tis associated	4	8			12 (4.7)
Grade:					
I	6	11	10	12	39 (15.4)
II	50	47	42	40	179 (70.8)
III	8	10	8	9	35 (13.8)
DNA:					
Diploid	48	50	40	45	183 (72.3)
Tetraploid	8	14	12	13	47 (18.6)
Aneuploid	8	4	8	3	23 (19.1)
Multiplicity:					
Single	22	28	19	19	88 (34.8)
Multiple	42	40	41	42	165 (65.2)
Tumor size (cm.):					
Less than 3	36	46	42	45	169 (66.8)
3 or More	28	22	18	16	84 (33.2)
Associated bilharziasis:					
Yes	20	26	28	21	95 (37.5)
No	44	42	32	40	158 (62.5)
Recurrence:					
De novo	40	40	34	33	147 (58.1)
Recurrent	24	28	26	28	106 (41.9)
Macroscopic picture:					
Papillary	58	66	53	52	229 (90.5)
Nodular solid	4	2	4	5	15 (5.9)
Other	2		3	4	9 (3.6)
Site:					
1	22	28	19	19	88 (34.8)
2	13	15	20	18	66 (26.1)
Multicentric	29	25	21	24	99 (39.1)

RESULTS

All patients were evaluable. Table 2 shows the major study results. Rates of recurrence in study arms 1 to 4 were 25% (16 patients), 17.6% (12), 36.7% (22) and 65.6% (40), respectively. These results were statistically significant with lower recurrence rates in the chemotherapy group than in controls ($p = 0.0002$) and in the pooled epirubicin groups than in the doxorubicin group ($p = 0.02$). However, recurrence rates per 100 patient months were 0.83, 0.60, 1.18 and 2.73 in arms 1 to 4, respectively. These results were statistically significant when comparing chemotherapy and control arms ($p < 0.001$), and pooled epirubicin and doxorubicin arms ($p < 0.05$). Between the 2 epirubicin groups there were no significant differences in simple recurrence rates but the difference was significant for recurrence rate per 100 patient months ($p < 0.05$). Curves showing interval to first recurrence were constructed using the Kaplan-Meier technique. Mean months to first recurrence in arms 1 to 4 was 16 (95% confidence interval 12.2 to 19.8), 15.4 (11.4 to 19.4), 18.9 (14.4 to 23.4) and 6.3 (5.2 to 7.4) months, respectively. The differences were statistically significant when comparing chemotherapy and control groups (log rank $p < 0.001$, fig. 1). There were no significant differences among the 3 chemotherapy arms (log rank $p = 0.05$). Table 3 lists recurrences in relation to tumor stage and grade. Rates of recurrence for pT1 and grade 2 tumors were greater in arm 3 than in the pooled epirubicin arms ($p = 0.01$ and 0.04, respectively) with no statistically significant difference between arms 1 and 2.

In arms 1 to 4 aneuploid tumors had higher recurrence rates than diploid and tetraploid tumors, comprising 17 of 23 cases (73.9%), 55 of 183 (30.1%) and 18 of 47 (38.3%), respectively ($p < 0.001$). For diploid tumors these rates were significantly lower in the chemotherapy arms than in controls ($p < 0.0001$). The pooled epirubicin groups had lower recurrence rates than the doxorubicin group but the results were not significant ($p > 0.05$). The relationship between other risk factors and recurrence rates in the 4 arms is beyond the scope of this study and it will be the subject of another report.

Progression to muscle invasive disease occurred in 21 patients (8.3%), including 7 (10.9%) in arm 1, 3 (4.4%) in arm 2, 6 (10%) in arm 3 and 5 (8.2%) in arm 4. Mean interval to progression in the 4 arms was 31 (95% confidence interval 22 to 40), 31 (18 to 44), 33 (26 to 40) and 37 (30 to 44) months, respectively. Kaplan-Meier survivorship curves were constructed to show interval to progression in the 4 arms and results were compared using the log rank test (fig. 2). Differences among the 4 groups and for each paired comparison regarding progression rates and interval to progression were not statistically significant (log rank $p = 0.6$).

In our study the overall toxicity rate was 26.6% or 51 of the 192 patients who received chemotherapy (table 4). Patients who received doxorubicin had a higher incidence of toxicity than those who received epirubicin ($p < 0.002$). Side effects were observed in 10 (15.6%), 16 (23.5%) and 25 (41.7%) patients in arms 1 to 3, respectively. Regarding the number of

TABLE 2. *Recurrence rates in the 4 study arms*

	Arm 1	Arm 2	Arm 3	Arm 4	Totals	p Value
No. pts./total No. (% recurrence)	16/64 (25)	12/68 (17.6)	22/60 (36.7)	40/61 (65.6)	90/253 (35.6)	1.9×10^{-4},* 0.02,† >0.05‡
Total mos. followup	1,920	2,006	1,860	1,830		
Recurrence rate/100 pt. mos.	0.83	0.60	1.18	2.73		<0.001,* <0.05†‡

* Arms 1, 2 and 3 versus 4.
† Arms 1 and 2 versus 3.
‡ Arm 1 versus 2.

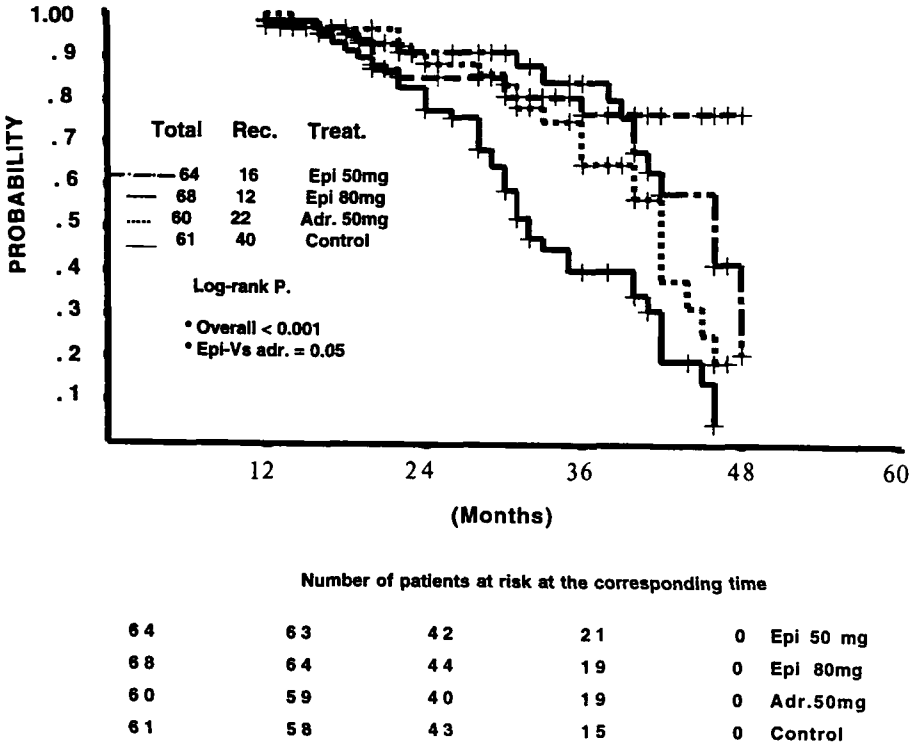


FIG. 1. Kaplan-Meier curves for interval to first recurrence (*Rec*). *Treat.*, treatment. *Epi*, epirubicin. *Adr*, doxorubicin.

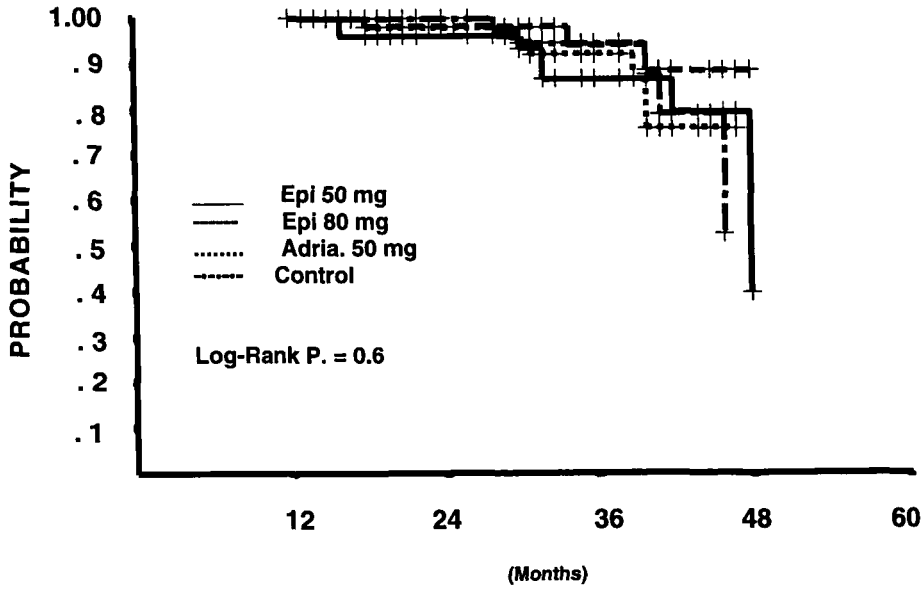
TABLE 3. *Tumor recurrence in relation to stage and grade*

	No. Arm 1	No. Arm 2	No. Arm 3	No. Arm 4	Total No. (%)	p Value
Stage:						
pTa	0	0	0	1	1 (3.4)	>0.05
pT1	15	10	22	39	86 (38.4)	2×10^{-8},* 0.01†
pTis	1	2			3 (25)	
Grade:						
I	0	2	3	5	10 (25.6)	>0.05
II	12	7	15	27	61 (34.1)	1×10^{-6},* 0.04†
III	4	3	4	8	19 (54.3)	>0.05
Grade III stage pT1/total (% recurrence)	4/6 (66.7)	3/8 (37.5)	4/7 (57.1)	8/8 (100)	19/29 (65.5)	<0.05,* >0.05†

* Arms 1, 2 and 3 versus 4.
† Arms 1 and 2 versus 3.

patients with toxicity, results were significant when comparing the high epirubicin dose and doxorubicin groups ($p = 0.04$) as well as the pooled epirubicin and doxorubicin groups. In the 3 chemotherapy groups toxicity developed in 88 (7.3%), 111 (8.7%) and 324 (28%) of 1,199, 1,280 and 1,118 instillations, respectively, with significant differences between the pooled epirubicin and doxorubicin groups ($p < 0.0001$) as well as between the high epirubicin dose and doxorubicin groups ($p < 0.05$).

Local side effects of the intravesical agents were classified into 2 grades depending on whether the patient was able to complete the instillation course: 1) mild toxicity was defined as urgency, frequency and burning voiding that were tolerated and did not require discontinuation of therapy provided that urinary tract infection was absent, and 2) severe toxicity was defined as untoward side effects requiring discontinuation of treatment permanently or for some time. Urinary tract infections developed in 1 patient in arm 1 and 1 in arm 2. These cases were diagnosed by urinalysis, urine culture and sensitivity tests. Appropriate antibiotics were given for 1 week and another culture was obtained thereafter, at which time urine was sterile. Mild chemical cystitis occurred in 5, 11 and 15 patients in arms 1 to 3, respectively, with a significant difference in favor of epirubicin when comparing the pooled epirubicin and doxorubicin groups ($p = 0.02$) but no significant difference between arms 2 and 3 ($p = 0.3$). Severe chemical cystitis occurred in 4, 5 and 6 patients, respectively, with no significant differences among the 3 groups ($p > 0.05$).



	TOTAL	No.Pts.	No.Censored	%Censored
Epi 50 mg	64	7	57	89.06
Epi 80 mg	68	3	65	95.59
Adria 50 mg	60	6	54	90.00
Control	61	5	56	91.80

FIG. 2. Kaplan-Meier curves for progression. *Epi*, epirubicin. *Adria.*, doxorubicin

TABLE 4. *Toxicity profile of 192 patients in study arms 1, 2 and 3*

	Arm 1	Arm 2	Arm 3	Totals	p Value
No. pts (%)	10 (15.6)	16 (23.5)	25 (41.7)	51 (26.6)	0.002,* 0.3,†, <0.04‡
No. with systemic toxicity (%)			3 (5)	3 (1.6)	<0.05*
No. with local symptoms:					
Mild	5	11	15	31 (16.1)	0.02,* >0.05,† 0.3‡
Severe	2	2	3	7 (3.6)	>0.05*†‡
Contracted bladder	1	1	2	4 (2.1)	
Hematuria	1	2	1	4 (2.1)	
Urinary tract infection	1		1	2 (1)	
Total No. (%)	10 (15.6)	16 (23.5)	22 (36.7)	48 (25)	0.01,* 0.3†
No. toxic episodes/total No. instillations (%)	88/1,199 (7.3)	111/1,280 (8.7)	324/1,118 (28)	523/3,597 (14.5)	<0.001,* >0.05†, <0.05‡

* Arms 1 and 2 versus 3.
† Arm 1 versus 2.
‡ Arm 2 versus 3.

Of the patients who received chemotherapy a contracted bladder developed in 4 (2.1%), including 1, 1 and 2 in arms 1 to 3, respectively. Cystectomy was performed in 2 of these cases. Hematuria developed in 1, 2 and 1 patient in the 3 chemotherapy arms, respectively, and all 4 patients responded well to conservative management. There was no significant difference between arms 1 and 2 regarding the number of patients with toxicity and the occurrence of toxicity in the total number of instillations ($p > 0.05$).

Three patients in the doxorubicin group had systemic side effects, including thrombocytopenia, fever in the absence of urinary tract infection and hypersensitivity reaction with bronchospasm in 1 each. Treatment involved discontinuation of doxorubicin, diphenhydramine and bronchial dilators in the case of hypersensitivity, and simple antipyretics in the case of fever. Discontinuation of doxorubicin was permanent in the cases of hypersensitivity and thrombocytopenia, and temporary (2 weeks) in the remaining case.

DISCUSSION

Superficial bladder tumors comprise a major sector of bladder cancer in the United States and Europe,[1] and only 20 to 30% of such tumors in Egypt.[2] However, the recent increasing incidence of superficial bladder carcinoma in Egypt can be attributed to a change in vesical carcinogenic mechanisms in the last 1 or 2 decades. Suggested causes include the increasing use of urine cytology and cystoscopy for early detection of suspected cases, improved treatment of schistosomiasis and increased environmental pollution with chem-

ical carcinogens. These causative factors have led to an increasing incidence of transitional cell carcinoma, of which the superficial papillary type is dominant.

There are 2 major goals of adjuvant intravesical therapy, namely, chemoprophylaxis and chemical resection.[11,12] Chemical resection aims at eradicating inaccessible, incompletely resected tumors, most frequently carcinoma in situ. However, the number of cases of associated carcinoma in situ in our study was small (12), and so this factor was beyond the scope of statistical significance. The rate of recurrence in this group was 25%, which is relatively low compared to the study of Smith et al.[13] However, this difference may be attributable to the brief followup in this particular group (mean 24 months).

In 1993 Oosterlinck et al performed the largest controlled study of epirubicin for prophylaxis.[14] A single instillation of 80 mg. epirubicin given immediately after transurethral bladder tumor resection decreased the recurrence rate by nearly 50% with the same trend noted in all tumor and patient variables examined. In the series of Melekos et al 60% of patients remained free of recurrence with multiple instillations of 50 mg. epirubicin at a mean followup of 32.9 months, while 41% of controls were recurrence-free.[15]

The recurrence-free rate in our study in the 2 epirubicin groups is higher than that in these 2 studies.[14,15] However, the rate in our study is lower than that in the series of Watanabe et al, in which only 11.3% of the patients had recurrence during a brief followup (1 to 20 months).[16] Recurrence-free rates for the doxorubicin and epirubicin groups are more or less comparable to those reported in 1992 by van der Meijden et al.[17]

For known prognostic factors and irrespective of the mode of therapy, our results confirmed those in the literature. Invasion of the lamina propria was a significant risk factor for our patients, since 38.4% with stage pT1 tumors but only 3.4% with stage pTa disease had recurrence. This observation is in accord with the study of Abel et al.[18] Regarding tumor grade, recurrence rates for grades I, II and III disease in all patients regardless of therapy were 25.6, 34 and 54.3%, respectively ($p = 0.02$), and these results confirm the observations of Carbin et al.[19] For grade II tumors the rates of recurrence were lower after chemotherapy ($p < 0.001$), supporting the findings of others.[19-21] No significant difference was observed between chemotherapy and control groups for grade III tumors, as in the series of Zincke et al.[7] Intravesical therapy did not provide any advantage over transurethral bladder tumor resection alone in patients with grade I or Ta tumors in whom the rates of recurrence were low (25.6 and 3.4%, respectively). DNA ploidy status had a unique value in our study, that is prediction of intravesical chemotherapy failure. Chemotherapy failure occurred in 90% of the cases in which DNA was converted from the diploid or tetraploid to the nontetraploid aneuploid pattern during therapy. Our results support the observation that chemotherapeutic drug instillation favorably alters the pattern of tumor recurrence.[11,14,17]

Interval to progression and progression rates were statistically comparable among the 4 arms (10.9, 4.4, 10 and 8.2%, respectively). These results confirmed the finding that intravesical therapy does not considerably affect the pattern of progression. However, a marginal difference was noted in arm 2, the group that received 80 mg. epirubicin.

Comparison of doxorubicin and epirubicin shows that epirubicin has better antitumor activity than doxorubicin, which appears to be a different conclusion than that of Shinohara et al, who described similar antitumor activity for the 2 drugs.[22] In our series a high concentration of epirubicin offered no statistically significant advantage over a lower concentration, which is in accord with the study of Burk et al.[23]

Regarding toxicity and side effects, most clinical studies have shown that the incidence of systemic toxicity of doxorubicin is rare, in the 2% range, and local side effects develop in 40 to 56% of cases.[20,24,25] Epirubicin is characterized by extremely rare toxic systemic effects but its local side effects may be the same in type and frequency as those reported for doxorubicin.[14,16,26] However, in our study the incidence of toxic side effects was significantly lower with epirubicin in the pooled group and arm 2 than with doxorubicin (15.6, 23.5 and 41.7%, respectively). The systemic side effects of doxorubicin were comparable to those in the study of Kurth et al.[25] The rare systemic toxicity of epirubicin and doxorubicin is related to low transurothelial absorption into the blood stream.[26,27] The incidence of contracted bladder was significantly higher than that in the literature but this rate was lower than in the series of Edsmyr et al.[28] However, contracted bladder was not attributed to the toxic effect of intravesical therapy only, but also to multiple tumor recurrences and resections, as in 2 patients after cystectomy for contracted bladder in whom the final histopathology evaluation demonstrated invasive bladder cancer. Association with bilharziasis may be a contributing factor in our study. In 1 of the 2 cases of cystectomy multiple bilharzial ova were found. Chemical cystitis developed in some cases after instillation 5. The frequency of this complication increased as the number of instillations increased, which confirms previous studies. Our series demonstrated a striking and unique observation, that is the rate of recurrence in the patients who had local side effects and completed the instillations was lower than that in those who did not have side effects.

CONCLUSIONS

Our study shows that epirubicin is a more optimal chemotherapeutic agent than its parent compound, doxorubicin. In high risk patients with superficial bladder transitional cell carcinoma adjuvant chemotherapy decreased the recurrence rate and recurrence rate per 100 patient months, and prolonged the interval between recurrences. A higher concentration of epirubicin (80 mg.) seems to be marginally more effective than a lower concentration (50 mg.) but this observation was beyond statistical significance.

Patients with grade II tumors are a major and heterogeneous group in whom the pattern of recurrence was favorably altered by chemotherapy. DNA flow cytometry was as sensitive as and even more sensitive than urine cytology for predicting tumor recurrence, progression and response to chemotherapy. Cystectomy may be a legitimate and safer option in those extremely high risk cases with grade III stage pT1 and aneuploid pT1 tumors.

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EDITORIAL COMMENT

In this study the 2 cytostatics, epirubicin and doxorubicin of the anthracycline family, were given intravesically after complete resection of stage Ta/T1 bladder carcinoma to prolong time to first recurrence and decrease the recurrence rate per 100 patient months (recurrence rate per year would have been more understandable) compared to transurethral resection alone. It is concluded that epirubicin has better efficacy than doxorubicin. This finding is surprising and I do not believe that the results justify the conclusion. In earlier studies in which cystostatics with proved therapeutic activity given intravesically were prospectively compared, none was superior (reference 25 in article).[1-4] For adjuvant chemotherapy doses of 50 and 80 mg. epirubicin, and 50 mg. doxorubicin were used. Although the pooled epirubicin results for time to first recurrence were superior to those of 50 mg. doxorubicin, 50 mg. epirubicin were not significantly better than 50 mg. doxorubicin ($p = 0.159$). Whereas for the end point of time to first recurrence no significant difference among the 3 chemotherapy arms was found, 80 mg. epirubicin significantly decreased the recurrence rate per 100 patient months compared to 50 mg. epirubicin. Thus, the superior results of the pooled epirubicin group are at least mainly due to the higher dose of epirubicin used in 1 arm. The 95% confidence interval for time to first recurrence is great in all treatment arms (15.0 to 37.4, 9.5 to 28.9, 24.6 to 50.1 and 52.3 to 77.3 in arms 1 to 4, respectively), although adjuvant treated patients undoubtedly do better than those treated with resection alone. The same observation holds true for recurrence rate per 100 patient months. No significant difference was found among the 4 treatment arms for progression to T2 disease or greater in this population of patients with an intermediate to high risk for progression. This finding confirms a recent combined analysis of patients treated by the European Organization for Research and Treatment of Cancer, Genitourinary Tract Cancer Cooperation Group and the Medical Research Council of the United Kingdom, showing no advantage of adjuvant chemotherapy over resection alone for preventing progression to T2 disease or greater.[5] It seems that neither adjuvant chemotherapy nor immunotherapy, compared to chemotherapy, can prevent progression to muscle invasive disease.[6,7] As even with the higher dose of epirubicin, significantly fewer cases and a significantly lower occurrence of local and systemic side effects were observed than after doxorubicin. Epirubicin may have advantages over doxorubicin. Although the finding of contracted bladder after adjuvant chemotherapy has been previously reported, 2.1% of patients (4 of 192) seems high and one wonders whether it can be explained by the high percent (38.5% or 74 of 192) of bladder tumors associated with bilharziasis.

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