



Bladder Cancer

Comparison of Three Schedules of Intravesical Epirubicin in Patients with Non–Muscle-Invasive Bladder Cancer

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Abstract

Objectives: To study the additive effect of either an early instillation or maintenance instillations of adjuvant intravesical epirubicin, as compared to the epirubicin “standard” treatment schedule only, in patients with non–muscle-invasive bladder cancer.

Methods: Patients with intermediate- and high-risk urothelial cell carcinoma of the bladder, except carcinoma in situ, were randomised for adjuvant intravesical instillations with 50 mg epirubicin/50 ml NaCl for 1 h. Group 1 received 4 weekly and 5 monthly instillations (standard schedule), group 2 received the same schedule as group 1, but with an additional instillation <48 h after transurethral resection of bladder tumour (TURBT), and group 3 received the same scheme as group 1, but with additional instillations at 9 and 12 mo (maintenance schedule). Standard follow-up was 5 yr and consisted of cystoscopy, cytology, and registration of adverse events.

Results: A total of 731 patients were eligible for quasi intention-to-treat analysis. Side-effects were minimal for all treatment groups. After 5-yr follow-up, respectively, 44.4%, 42.7%, and 45.0% (log-rank test, $p = 0.712$) of the patients in groups 1, 2, and 3 were recurrence free, and 90.0%, 87.7%, and 88.2% (log-rank test, $p = 0.593$) of the patients, respectively, were progression free.

Conclusions: In the quasi intention-to-treat analysis there is no difference in the 5-yr recurrence-free period between the treatment groups, despite one instillation within 48 h of TURBT or two maintenance instillations up to 1 yr, in addition to the “standard” schedule.

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1. Introduction

Standard therapy for non-muscle-invasive bladder cancer (NMIBC) is transurethral resection (TURBT) and adjuvant intravesical instillations to reduce the risk of recurrence or progression. The choice of adjuvant treatment is based on prognostic factors [1]. In patients with low-risk tumours an immediate (early) post-TURBT instillation with a chemotherapeutic agent significantly lowers the recurrence rate in the first few years and is considered sufficient as adjuvant treatment for this risk group. Patients with intermediate-risk tumours benefit from a single immediate instillation of chemotherapy but need a further course of adjuvant chemotherapy instillations for 4–8 wk, or immunotherapy with bacillus Calmette-Guérin (BCG) [2]. BCG is indicated for patients with high-risk tumours.

Epirubicin (4' epi-doxorubicin) is a chemotherapeutic drug with a good tolerability profile and efficacy in the prevention of recurrences of NMIBC. In a multicentre randomised trial with 431 patients with NMIBC (Ta–T1), a single immediate instillation of epirubicin was compared to sterile water as placebo and showed a significantly lower recurrence rate in patients treated with epirubicin [3]. The European Organization for Research and Treatment of Cancer (EORTC) randomised 957 patients with intermediate- and high-risk NMIBC for either adjuvant treatment with BCG, BCG and isoniazid, or epirubicin [4], and found that patients treated with either BCG regimen had a longer recurrence-free survival as compared to those treated with epirubicin. However, toxicity with epirubicin was markedly lower. Despite the superiority of BCG in patients with high-risk NMIBC [4], its superiority over epirubicin in patients with intermediate-risk NMIBC is not proven. Epirubicin is especially effective in patients with low- and intermediate-risk NMIBC who have a low risk of progression [3].

To investigate the hypothesis whether there is a more efficient instillation scheme of epirubicin, we performed a study comparing three schedules of adjuvant intravesical epirubicin in the treatment of patients with intermediate- and high-risk NMIBC, with the exception of patients with carcinoma in situ (CIS).

2. Patients and methods

This is a multicentre prospective randomised phase 3 trial in which 23 Dutch hospitals participated. After ethical committee approval in each of the participating hospitals, the study was conducted in accordance with the ethical

standards laid down in the Declaration of Helsinki amended version 1989.

2.1. Patient selection

Patients ≤ 85 yr old with a histologically proven solitary pT1 tumour, or multiple primary, or recurrent T1 or Ta G1–3 urothelial cell carcinoma (UCC) of the bladder, in whom complete transurethral resection was possible, were included. Tumours were classified according to the recommendations of the World Health Organization (WHO) [5] and the International Union Against Cancer [6]. Patients may have received intravesical therapy before, but not epirubicin or therapy within 6 mo of study entry. Informed consent was obtained before TURBT. Patients with pathologically confirmed primary solitary Ta tumours, CIS, or tumours $\geq T2$ were excluded. Other exclusion criteria were concurrent malignancy (except basal cell carcinoma or squamous cell carcinoma of the skin), history of other malignancy with a disease-free interval ≤ 5 yr, expected poor compliance, WHO performance status > 2 , uncontrollable urinary tract infection, any previous systemic cancer therapy or radiotherapy, localisation of UCC in prostatic urethra or upper urinary tract, pregnancy or lactation or women of reproductive age who refuse to take adequate contraceptive measures, congenital or acquired immunodeficiency, known hypersensitivity to anthracyclines, or concurrent treatment with an investigational drug.

2.2. Treatment schedule

After complete transurethral resection of clinical NMIBC, patients were randomised on the day of TURBT for one of three treatment schedules. Intravesical instillations of 50 mg epirubicin in 50 ml saline were given for 1 h. Group 1 (“standard” schedule) started the first of four weekly and five monthly instillations within 14 d after TURBT (duration 6 mo, 9 instillations). Group 2 received the same schedule as group 1, preceded by a single dose within 48 h of TURBT (duration 6 mo, 10 instillations). Group 3 received the same schedule as group 1, with two additional 3-monthly instillations (duration 12 mo, 11 instillations). If necessary, delay of an instillation or dose modification was at the investigator’s discretion and documented. If a recurrence was observed during the treatment period, it was resected without modification of the treatment schedule. Patients went off-study after a second recurrence during the instillation period, the first recurrence after completion of treatment, after 5-yr disease-free survival, occurrence of CIS, or UCC of the prostatic urethra or upper urinary tract or distant metastasis.

2.3. Follow-up and evaluation of therapy

Urine cytology and cystoscopy were done every 3 mo for the first year, every 4 mo for the second and third years, and every 6 mo for the fourth and fifth years after TURBT. All visible lesions had to be resected, with recurrence confirmed by histologic examination. Adverse events were recorded with information on duration, severity, relation to study treatment, start of concomitant medication, and outcome of the event.

2.4. Objectives and statistical analysis

The study was designed to compare the effect of epirubicin in three different treatment schedules with respect to efficacy (recurrence-free rate, progression-free rate, duration of disease-free interval) and safety (incidence and severity of side-effects). To detect a true ratio of median time to first recurrence, 1.75/2.5 (yr) between any of the three treatment groups at error rates of $\alpha = 0.05$ and $\beta = 0.10$, a total of 247 patients had to be entered in each treatment group. Two patient groups were identified for the efficacy analysis. The intention-to-treat (ITT) analysis, the primary analysis, was performed with all eligible patients who were randomised, a quasi-ITT approach [7]. The per-protocol analysis, the secondary analysis according to the protocol, was performed with all eligible patients who followed their complete instillation schedule. Time to recurrence was defined as the time between TURBT and first recurrence after completion of treatment, or second recurrence during treatment. Progression was defined as muscle-invasive disease, CIS, UCC outside the bladder, or distant metastasis or death related to UCC. Time to progression was defined as the time between TURBT and first progression. Recurrence-free rate was defined as the percentage of patients with no recurrence in the total study population in follow-up at a certain point in time. Progression-free rate was defined as the percentage of patients with no progression in the total study population in follow-up at a certain point in time. Duration of disease-free interval was estimated according to the Kaplan-Meier method and comparison between treatment groups by means of the log-rank test. Observed sample percentages in the safety analyses were compared between treatment groups by means of a χ^2 test. Statistical analyses were done in SPSS version 14.0.

3. Results

3.1. Patient and tumour characteristics

Between April 1998 and April 2004, 1000 patients were randomised for the study, of whom 731 (73%)

Table 1 – Patient ineligibility

	Group			Total (%)
	1	2	3	
No. of patients	101	91	77	269
Primary solitary Ta	20	17	14	51 (19)
T0	12	18	14	44 (16)
$\geq T2$	18	22	17	57 (21)
CIS	15	8	12	35 (13)
Other malignancy ≤ 5 yr	6	1	8	15 (6)
Intravesical therapy < 6 mo	6	4	2	12 (4)
Patient refusal	4	5	2	11 (4)
Other	20	16	8	44 (16)

CIS = carcinoma in situ.

Table 2 – Patient and tumour characteristics of eligible patients at study entry

	Group			Total (%)
	1	2	3	
No. of patients	239	238	254	731
No. of tumours				
Single	47	43	56	146 (20)
Multiple	192	195	198	585 (80)
Prior recurrence rate				
Primary	114	109	131	354 (48)
Recurrence ≤ 1 yr	38	55	50	143 (20)
Recurrence ≥ 1 yr	87	74	73	234 (32)
T category				
Ta	190	196	189	575 (79)
T1	49	42	65	156 (21)
History of CIS	3	2	4	9 (1)
Grade				
1	108	101	96	305 (42)
2	108	109	126	343 (47)
3	21	26	31	78 (11)
Previous treatment				
Intravesical instillation	40	36	31	107 (15)
TURBT only	81	82	86	249 (34)

CIS = carcinoma in situ; TURBT = transurethral resection of bladder tumour.

were eligible. Originally, 815 patients were to be included, taking into account a 10% dropout rate, but during the study the dropout rate proved to be much higher, and the ethical committee approved increasing the number of study patients. The main reason for this was that histology, which was known after the time point of randomisation, did not correspond with the clinical appearance of a lesion (Table 1). Patient characteristics were comparable among the treatment groups (Table 2). The male-to-female ratio was 4:1, the mean age 67 yr (range: 33–84 yr). Primary, multiple, pTa, and grade 1–2 tumours occurred most often.

3.2. Safety

Of 1000 patients, 829 received at least one instillation of epirubicin. Fifty-seven patients (7%) had to stop the instillations because of local or systemic side-effects (Table 3). Haematuria was observed significantly more in the immediate instillation group (Pearson χ^2 , $p = 0.03$). Other side-effects were not significantly different between treatment groups. Thirteen percent of the patients experienced systemic side-effects. The most frequent systemic side-effects were tiredness, fever, nausea, headache, and abdominal pain.

Table 3 – Side-effects of epirubicin by treatment group

	Group 1 (%)	Group 2 (%)	Group 3 (%)	Total (%)
No. of patients	266	286	277	829
Bacterial cystitis				
Never	205 (77)	226 (79)	215 (78)	646 (78)
Not requiring delay	46 (17)	37 (13)	40 (14)	123 (15)
Requiring delay	12 (5)	22 (8)	20 (7)	54 (7)
Requiring stop	3 (1)	1 (1)	2 (1)	6 (1)
Chemical cystitis				
Never	182 (68)	191 (67)	211 (76)	584 (70)
Not requiring delay	72 (27)	77 (27)	54 (20)	203 (25)
Requiring delay	6 (2)	7 (2)	4 (1)	17 (2)
Requiring stop	6 (2)	11 (4)	8 (3)	25 (3)
Haematuria				
Never	230 (87)	232 (81)	246 (89)	708 (85)
Not requiring delay	32 (12)	41 (14)	23 (8)	96 (12)
Requiring delay	2 (1)	12 (4)	2 (1)	16 (2)
Requiring stop	2 (1)	1 (1)	5 (2)	8 (1)
Other local side-effects				
Never	244 (92)	259 (91)	252 (91)	755 (91)
Not requiring delay	18 (7)	16 (6)	21 (8)	55 (7)
Requiring delay	2 (1)	4 (1)	2 (1)	8 (1)
Requiring stop	2 (1)	7 (2)	1 (1)	10 (1)
Systemic side-effects				
Never	232 (87)	246 (86)	239 (86)	717 (87)
Not requiring delay	29 (11)	30 (11)	32 (12)	91 (11)
Requiring delay	3 (1)	6 (2)	3 (1)	12 (1)
Requiring stop	2 (1)	4 (1)	2 (1)	8 (1)
General delay or stop				
No delay or stop	227 (85)	224 (78)	216 (78)	667 (81)
Delay	11 (4)	17 (6)	15 (5)	43 (5)
Stop	28 (11)	45 (16)	46 (17)	119 (14)

3.3. Efficacy

A total of 731 patients were eligible for quasi-ITT analysis, of whom 531 completed the entire instillation schedule per protocol. Patients of groups 1, 2, and 3 received on average 8.4 of 9 (SD 1.9), 8.9 of 10 (SD 2.5), and 10.0 of 11 (SD 2.4) instillations, respectively. In the quasi-ITT analysis, 44.4%, 42.7%, and 45.0% (mean: 44.1%, 344 events) of the patients from, respectively, groups 1, 2, and 3 were 5-yr recurrence free (log-rank test, $p = 0.712$). No significant differences were found with pair-wise comparison. Median follow-up was 2.07 yr. Median recurrence-free survival was 3.2 yr (range: 2.4–4.1 yr). Kaplan-Meier curves for time to recurrence are presented in Fig. 1.

Progression was seen in 48 patients; 25 patients (3.4%) had muscle-invasive disease and 23 patients (3.1%) had CIS. UCC outside the bladder, distant metastases, or death related to UCC were not observed. In the quasi-ITT analysis, the overall 5-yr progression-free rate was 88.6%, and specified for groups 1, 2, and 3, respectively, 90.0%, 87.7%, and 88.2% (log-rank test, $p = 0.593$).

Of all patients in group 2, 168 (68%) received an immediate instillation <24 h after TURBT, and 72 patients (30%) ≥ 24 h and <48 h after TURBT. Four patients received no instillations. In the quasi-ITT analysis, the 5-yr recurrence-free rates for patients treated <24 h, or ≥ 24 h and <48 h after TURBT were 41.5% and 47.3% (log-rank test, $p = 0.401$), respectively, and the 5-yr progression-free rates were, respectively, 91.2% and 81.6% (log-rank test, $p = 0.093$).

4. Discussion

The objective of this trial was to study the additive effect of either an early instillation or two maintenance instillations of adjuvant intravesical epirubicin, as compared to the epirubicin “standard” treatment schedule only, in an intermediate- and high-risk group of patients with NMIBC. Patients with CIS were excluded because treatment with BCG instillations for patients with CIS became state-of-the-art by the end of the last decade. At that time, the greater benefit of BCG over chemotherapy for

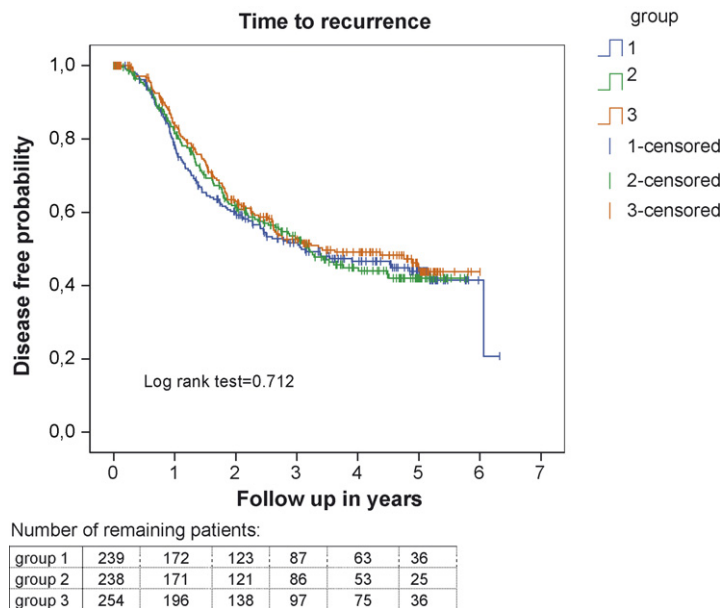


Fig. 1 – Time to recurrence by treatment group for patients in the quasi intention-to-treat analysis.

patients with high-risk papillary lesions was not as obvious as today.

Comparing studies on intravesical chemotherapy often is troublesome because of differences in dose (mg), concentration (mg/ml), and volume (ml) used, the dwell time, and the volume and pH of the urine [8]. Moreover, treatment schedule and frequency will influence therapy efficacy. Finally, additional confounding factors can be the study size, variability in duration of follow-up, and differences in patients' characteristics [1,9]. The establishment of the optimal treatment regimen for epirubicin is also hampered by differences in dose, concentration, instillation schedule, frequency of instillations [10], and the small size of some trials.

Kuroda et al [11] randomised 622 patients with Ta-T1 G1-2 NMIBC for adjuvant treatment with 17 doses of epirubicin 20 mg/40 ml in 12 mo, 12 doses of epirubicin 30 mg/40 ml in 7 mo, or 9 doses of epirubicin 40 mg/40 ml in 4 mo. At 2-yr follow-up, the recurrence-free rates were 48.7%, 55.1%, and 60.1%, respectively, showing the greatest effect by the highest dose regimen, administered over a short period of time. Koga et al [12] randomised 171 patients with Ta-T1 G1-3 NMIBC for either short-term (<24 h, days 2/3, week 1 and 2, 5 times every 2 wk) or long-term (short-term schedule + 9 times monthly) 30 mg/30 ml adjuvant epirubicin. At 3-yr follow-up, long-term treatment was more effective than short-term treatment, with recurrence-free rates of 85.2% and 63.9%, respectively. Another study included 148 patients with all stages and grades of NMIBC, without a difference in

efficacy between patients treated with 6 instillations in 4 wk (short-term), or the same treatment with 11 additional monthly instillations (long-term) of epirubicin 40 mg/40 ml [13]. At 2-yr follow-up, 75.1% and 77.2% were recurrence free, respectively. Nomata et al treated 125 patients with Ta-T1 G1-2 NMIBC with 30 mg/30 ml epirubicin, either 19 times over 1 yr or 12 times over 5 mo [14], with, respectively, 48.5% and 55.1% of the patients recurrence free at 3-yr follow-up, which was a nonsignificant difference. In all, these data show discrepancies in study outcome among a variety of schedules used, including highly differing definitions of short-term treatment and long-term treatment. The only improvement in results seems to be caused by a higher dose (40 mg/40 ml [11]).

By using per-protocol analysis instead of ITT analysis, 45.2%, 46.8%, and 55.0% of the patients from, respectively, groups 1, 2, and 3 were recurrence free at 5 yr (log-rank test, $p = 0.041$), with a statistically significant difference ($p = 0.012$) on pairwise comparison of groups 1 and 3, but no differences between the other groups. However, we need to be careful with conclusions based on per-protocol analysis because the difference was small and we had difficulties in achieving enough statistical power due to the high number of ineligible patients. The power to detect a true ratio of median time to first recurrence times of 1.75/2.5 (yr) between any of the three treatment groups at error rates of $\alpha = 0.05$, was calculated at 84% in the per-protocol analyses (smallest group contained 176 patients) and at 93% in the ITT analysis (smallest group

contained 238 patients). A disadvantage of per-protocol analysis is the occurrence of selection bias. Instead, one could question whether two additional instillations up to 1 yr would be able to change the 5-yr recurrence-free estimate. In other trials of epirubicin, maintenance instillations were often applied monthly, mostly for no longer than 1 yr, with no differences in recurrence-free estimates [11–14]. In a recent study comparing 6 weekly instillations of mitomycin C to 6 weekly instillations followed by monthly instillations during 3 yr (42 instillations), there was a large decrease in the percent of patients with recurrence in the group receiving 3 yr of treatment, 25.7% versus 10.5% ($p = 0.0006$) [15]. However, results for mitomycin C are also contradictory. Two other studies also compared short-term versus long-term (3 yr, 42 instillations) mitomycin C, but in both studies the short-term and the long-term schedules were different from the study by Friedrich et al [15], with no differences in the percent of patients with recurrence [16,17].

The European Association of Urology (EAU) guidelines recommend to give one immediate, postoperative instillation with a chemotherapeutic drug in every patient with NMIBC [1]. This decreases the risk of recurrence by approximately 12%, as demonstrated in a meta-analysis of seven trials involving 1476 patients, with median follow-up of 3.4 yr [2]. In three of these trials epirubicin was studied [3,18,19], but no drug was found to be superior with regard to efficacy. Regarding an immediate instillation as part of a treatment schedule, two parallel studies by the EORTC demonstrated that intravesical chemotherapy administered monthly for 1 yr versus 6 mo resulted in similar recurrence rates when the first instillation was given immediately after TURBT [20]. But again, data are conflicting (above) [12,14].

Timing of the instillation appears crucial, and all drugs in the meta-analysis were administered within 24 h, generally immediately after TURBT or within 6 h. Pan et al studied inhibition of murine bladder tumour cell implantation by the use of thiotepa immediately, <1 h, and <24 h after tumour cell inoculation and found that the control and <24 h group had significantly higher tumour implantation rates than the immediate and <1 h group [21]. Kaasinen et al found, in their retrospective analysis, a doubling in the relative risk of recurrence when the instillation was not given on the same day as the TURBT [22]. In our trial, 168 patients (68%) of group 2 received the first instillation <24 h and 72 patients (30%) <48 h after TURBT, but the 5-yr recurrence-free rates (41.5% and 47.3%,

respectively) and progression-free rates were comparable. There was no significant difference in the occurrence of haematuria between group 2 and the other two groups when leaving out the immediate instillation in the analysis. When looking at the first instillation only, the significant difference is probably caused by the performance of TURBT and may be due to the first instillation within 48 h, when the bladder walls of these patients had little time to recover. There was no increase in the number of patients in group 2 requiring instillation cessation.

5. Conclusions

The three treatment schedules of epirubicin were well tolerated, but haematuria occurred more in the immediate instillation group. In reducing recurrence, the “standard” treatment schedule was as effective as the same schedule with an additional immediate post-TURBT instillation, or additional maintenance instillations. The wide timing range of the first instillation (up to 48 h) in the immediate instillation group and the low number of additional instillations in the maintenance group may explain the lack of additional efficacy in these two groups as compared to the standard therapy group, even though we could not find, in the immediate instillation group, significant differences in a subgroup of patients treated in <24 h as compared to those treated ≥ 24 h and <48 h.

Conflicts of interest

The authors have nothing to disclose.

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