

Alternating Mitomycin C and BCG Instillations versus BCG Alone in Treatment of Carcinoma in Situ of the Urinary Bladder: A Nordic Study

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Abstract

Objectives: To evaluate whether, in patients with carcinoma in situ (CIS) of the urinary bladder, alternating instillation therapy with mitomycin C (MMC) and bacillus Calmette-Guerin (BCG) was more effective and less toxic than conventional BCG monotherapy.

Methods: Patients were stratified prospectively for primary, secondary, and concomitant CIS and randomized to one of two regimens. Patients in the alternating group received six weekly intravesical instillations of MMC 40 mg, followed by alternating monthly instillations of BCG 120 mg and MMC for one year. In the monotherapy group, only BCG was instilled on the same schedule.

Results: Of 323 enrolled patients, 304 were eligible for analysis. After an overall median follow-up of 56 months, the Kaplan–Meier disease-free estimate for BCG monotherapy was significantly better than that for alternating therapy ($p = 0.03$; log rank test). Risk for progression appeared lower in the BCG monotherapy group ($p = 0.07$), but no differences existed in survival. Besides the regimen, CIS category also predicted outcome to some extent. BCG monotherapy caused significantly more local side-effects and premature cessation of instillation treatment than did the alternating therapy. However, no differences were observed in the number of serious side-effects.

Conclusion: One-year BCG monotherapy was more effective than the alternating therapy for reducing recurrence and compared well with the best regimens reported from substantially smaller series. The alternating therapy was better tolerated.

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1. Introduction

Carcinoma in situ (CIS) of the urinary bladder presents clinically in three different forms [1]: Primary CIS appears de novo in patients with no prior history of bladder cancer, secondary CIS occurs during follow-up in previously treated urothelial carcinoma, and concomitant CIS appears concurrently with a superficial

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papillary tumor or a nodular invasive tumor. In two large Scandinavian series [2,3] with a total of 790 patients, primary CIS accounted for 1–4% of the primary tumors, whereas concomitant CIS occurred in 13–20%. However, because more than half the tumors with concomitant CIS were muscle-invasive at diagnosis, only 5% of primary carcinomas comprised superficial Ta-T1 tumors with concomitant CIS lesions, which, like primary CIS, are amenable to endovesical instillation therapy. Because of the low incidence, most series are small and therefore frequently analyzed together with other forms of superficial bladder carcinoma.

Unlike most superficial urothelial tumors, CIS is an aggressive malignancy with a variable and unpredictable natural history and a considerable potential for invasiveness. A progression rate as high as 54% within five years is based on 14 series comprising 382 patients with untreated CIS [4–6]. Based on limited data, virtually all patients may eventually, without appropriate treatment, experience progression [5].

Bacillus Calmette-Guerin (BCG) instillation therapy is generally regarded as the most effective treatment for high-grade superficial bladder cancer and CIS. Proponents of BCG therapy have claimed that BCG therapy reduces progression and mortality better than do the less toxic chemotherapy instillations [7–10]. In contrast to a meta-analysis of the American Urological Association (AUA) 1999 [12], this view is now supported by two more recent meta-analyses [11,13]. However, not even the newer analyses allowed conclusions to be drawn about the impact of BCG therapy on disease-specific death rates. Some limited data additionally suggest that if patients are followed long enough and development of upper urinary tract tumors is taken into account, the natural progression rate of CIS is not necessarily much affected by BCG therapy [14].

Preliminary results at the time of our study design suggested that a combination therapy with alternating instillations of mitomycin C (MMC) and BCG was superior to MMC monotherapy and caused fewer side-effects than has been reported with BCG monotherapy [15,16]. In the present trial we evaluated whether a similar combination regimen with minor modifications was more effective and less toxic than BCG monotherapy.

2. Patients and methods

From December 1992 to December 1997, 323 patients were enrolled at 34 urological units in Finland (95 patients), Norway (7), and Sweden (221) in a prospective randomized multicenter study conducted by the Nordic Urothelial Cancer Group. The study

protocol was designed to meet the criteria of the Helsinki declaration, including written informed consent signed by the patients.

2.1. Eligibility criteria

Our inclusion criteria were histologically verified high-grade primary, secondary, or concomitant (with pTa or pT1 tumor) carcinoma in situ of the urinary bladder, with complete eradication of all visible pTa or pT1 tumors in case of concomitant CIS. Patients who previously had undergone instillation therapies were also eligible for study inclusion if that therapy ended more than six months earlier. Patients should have had WHO performance status 0–2. Exclusion criteria were CIS in other parts of the urinary tract, previous radiotherapy or systemic chemotherapy, other conditions impairing the immune defense system, or preceding or concurrent malignancy other than carcinoma in situ of the cervix or adequately treated basal cell carcinoma of the skin.

2.2. Randomization, treatment and follow-up

Patients were stratified by nationality and CIS category before being randomized to either of two regimens. Patients in the alternating therapy group received six weekly intravesical instillations of mitomycin C (MMC) 40 mg in 50 ml of saline, followed by alternating instillations of BCG (Connaught) 120 mg in 50 ml saline and MMC monthly for up to one year. Patients in the monotherapy group received six weekly BCG instillations, followed by monthly BCG instillations for up to one year (Fig. 1). The first instillation was given no earlier than two weeks after the diagnostic transurethral procedure. Patients were evaluated every three months during the first two years and thereafter according to local practice. The evaluation involved cytology, cystoscopy, and biopsies of suspicious lesions.

2.3. Study objectives

Because our study aimed to explore whether an alternating instillation treatment with MMC and BCG would be more effective and cause fewer side-effects than BCG monotherapy, our primary endpoints were disease-free interval and time to progression. Secondary endpoints were survival and side-effects. In addition, complete response (CR) was recorded at the initial evaluation at three months and at one year to allow comparisons with other trials and with response rates applied in our sample-size calculations. An additional endpoint, treatment failure, was constructed to illustrate the long-term effect of the whole one-year instillation period. Recurrence (or persistent disease) was defined as biopsy-confirmed CIS or non-invasive papillary carcinoma (pTa), or malignant cytology, and progression was defined as pT1 tumor or more advanced disease. If progression was the first event without preceding occurrence of CIS, it was also included as an event in the disease-free analysis. Patients were considered to have CR at one year if they had no progression during the first nine months and no

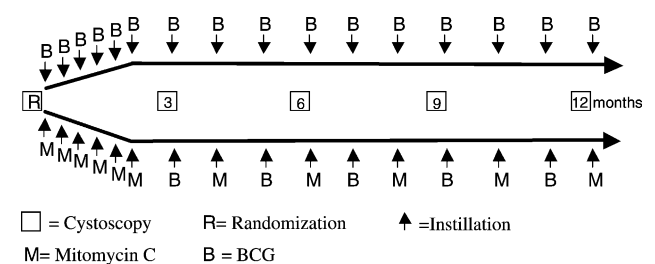


Fig. 1. Instillation schedule.

recurrent/persistent disease or progression at 12 ± 3 months. Treatment failure was defined as progression or change in therapy resulting from recurrence or side-effects during the first year, or alternatively, as recurrence, progression, or change in therapy after the first year. Reasons and time-point for cessation of instillation treatment were documented. Severity of local and systemic side-effects was recorded at 3 months and 12 months.

2.4. Statistical analysis

For sample-size estimation, we initially assumed a complete response rate of 80% for the alternating therapy and 65% for BCG monotherapy at one year. With comparison of binomial proportions by a two-tailed test with a power of 80%, at least 138 eligible patients were required in each arm to detect a 15% difference at a significance level of 0.05. Considering patients lost to follow-up, the estimated number required rises to 150 patients in each arm. Approximately the same number of patients is needed if similar assumptions are applied to the sample-size estimation for materials analyzed with the log rank test [17].

Results were analyzed with standard statistical software (Statistica'98 Edition and SPSS release 10.0.7). χ^2 statistics were applied in cross-tabulations. The Student's *t*-test was used to compare the means of normally distributed variables between the two treatment groups. Otherwise, the Mann–Whitney *U*-test was used. All time-related endpoints with respect to treatment were analyzed by the Kaplan–Meier technique and the log rank test [18,19]. As for the method of censoring, deaths from other causes than CIS were considered as censored in the analysis of disease-free interval, time to progression, time to treatment failure, and disease-specific survival. The significance of all the factors that could explain outcome of time-related endpoints was tested with the Cox proportional hazards regression model [20]. The explanatory variables tested included country, gender, age, regimen, CIS category, cytology, number of positive biopsies, and presence/absence of previous irritative symptoms. With robust assumptions of normality (of the distribution of sample means) and linearity, the scores of severity of local and systemic side-effects were tested with the unpaired Student's *t*-test and linear regression. *p*-value ≤ 0.05 was considered statistically significant.

3. Results

Of 323 enrolled patients, 304 were considered evaluable for the actual analysis. Of 19 (5.8%) excluded patients, six belonged to the alternating group and 12 to the monotherapy group, while grouping data were missing in one ($p = 0.2$; Yates corrected χ^2). Nine of the excluded patients were ineligible. The reasons for ineligibility were other preceding or concurrent malignancy in two patients, invasive or metastatic disease in two, in addition to single cases of other intervening drug therapy, double randomization, too-recent preceding instillation therapy, CIS detected in the urethra, and missing findings of CIS in a biopsy specimen. In the remaining nine patients, the reason for exclusion was the absence of (despite remainders) inclusion or all follow-up data or both in four patients and an early protocol violation with the start of instil-

Table 1

Patient characteristics

	Number of patients	
	Alternating therapy ^a	BCG monotherapy ^a
Randomized ^b	165	157
Eligible for analysis	159	145
Country		
Sweden	107	103
Finland	47	41
Norway	5	1
Sex		
Male	125	119
Female	34	26
Age (mean in years)	71.0	69.9
Primary CIS	47	44
Secondary CIS	68	61
Stage of preceding tumor pTa/pT1/unclear or missing	40/26/2	35/22/4
Grade of preceding tumor G1/G2/G3/unclear or missing	6/39/21/2	7/37/13/4
Concomitant CIS	44	40
Stage of concurrent tumor pTa/pT1/missing	17/21/6	20/16/4
Grade of concurrent tumor G1/G2/G3/missing	2/11/25/6	1/16/19/4
Cytology		
Positive	120	111
Negative	10	8
Inadequate	19	18
Cytology missing	10	8
Number of positive biopsies per patient (mean)	2.3	2.3

^a All differences in distribution of patient characteristics N.S.

^b Grouping data missing for one ineligible patient.

lations in five. Apart from the slight imbalance in the number of eligible patients, patient characteristics were evenly distributed between the two groups (Table 1). The overall median follow-up time was 56.3 months (range, 1.9–97.3 months).

3.1. Complete response (CR)

At initial evaluation at three months, 120 of 145 patients (82.8%) in the monotherapy arm and 119 of 159 patients (74.8%) in the alternating arm were in complete remission. This difference was not significant ($p = 0.6$; Yates corrected χ^2).

At one year, 106 of 136 evaluable patients (77.9%) in the monotherapy group and 116 of 147 (78.9%) in the alternating group had CR. Assessment of response was not possible because of early withdrawal for unrelated cause in 14 patients and because of incomplete data in seven.

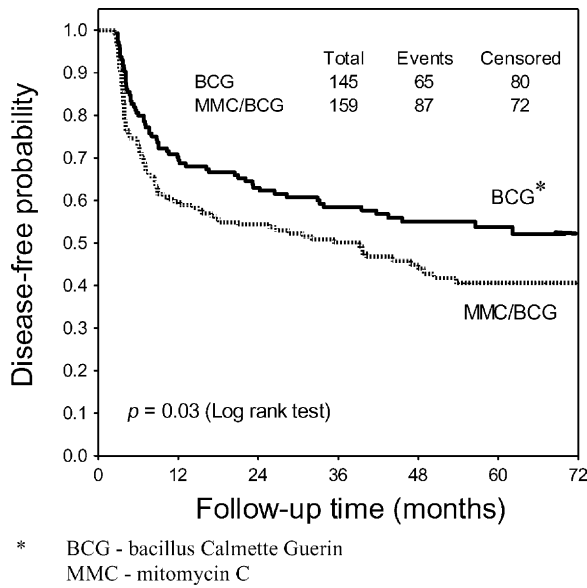


Fig. 2. Disease-free interval in both treatment groups: BCG monotherapy vs. alternating therapy (MMC/BCG).

3.2. Disease-free interval

Kaplan–Meier analysis showed a statistically significant difference in disease-free interval in favor of the BCG monotherapy group ($p = 0.03$; log rank test) (Fig. 2). Whereas the median disease-free interval was not by then reached in the monotherapy arm, it was 39.1 months (95% confidence interval [CI], 17.4–60.9 months) in the alternating arm. At a follow-up time of 60 months, the Kaplan–Meier disease-free estimates were 40.7% and 53.8% for the alternating and monotherapy groups. As for various CIS categories, some—albeit not significant—differences were evident, with the disease-free probability being highest among patients with concomitant CIS and lowest among those with primary CIS.

3.3. Time to progression

The estimates of non-progression showed a tendency towards a better outcome for the BCG monotherapy group ($p = 0.07$; log rank test) (Fig. 3A). Median time to progression was not achieved in either of the groups, due to the low number of patients showing progression. Probability of non-progression appeared different among various CIS categories ($p = 0.05$; log rank test): probability of avoiding progression was highest among patients with primary CIS and lowest among those with concomitant CIS (Fig. 3B).

Approximately half of 54 progressions were pT1 tumors, with the proportion of pT1 versus more advanced disease similar in both treatment groups and in each CIS category. Apart from a more frequent use of radiotherapy in the alternating group, similar

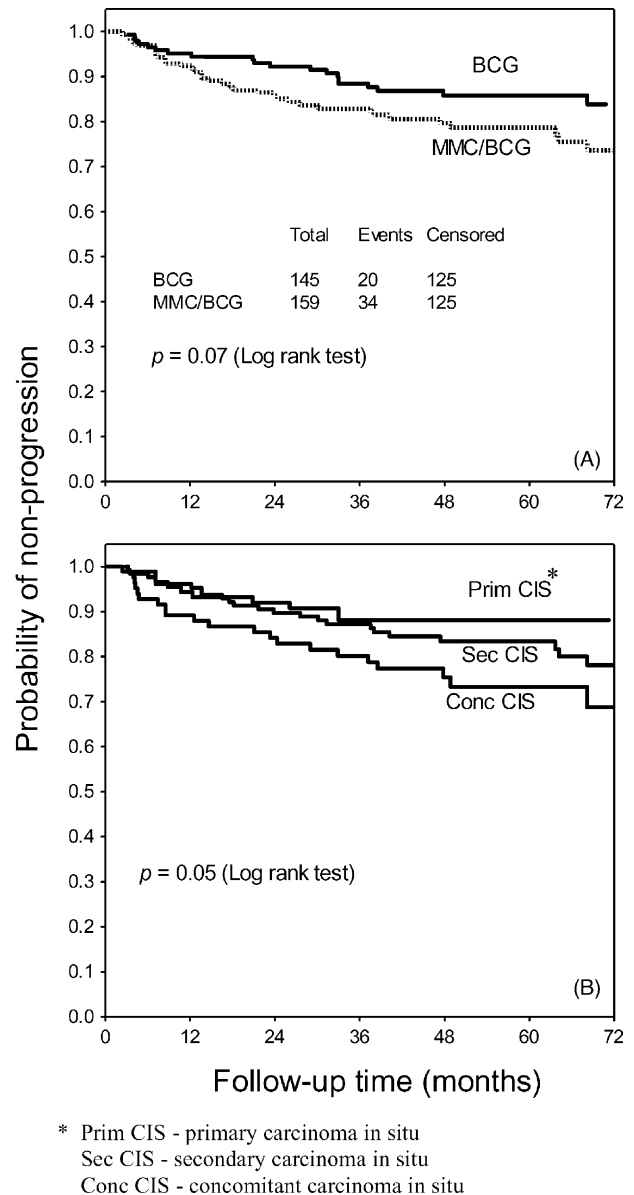


Fig. 3. Time to progression, (A) in both treatment groups, and (B) among various CIS categories.

therapeutic approaches were applied to patients with progressions in both groups.

3.4. Treatment failure

Failure-free estimates (Fig. 4A) showed a tendency towards a better outcome in the monotherapy group. Median time to failure was 50.4 months in the alternating group, whereas it had not yet been attained in the monotherapy group.

Approximately half the patients with early recurrence (excluding progressions) during the one-year therapy have remained free of disease thus far. These patients comprised 12% of all patients and explained the slight elevation in the failure-free plots compared to

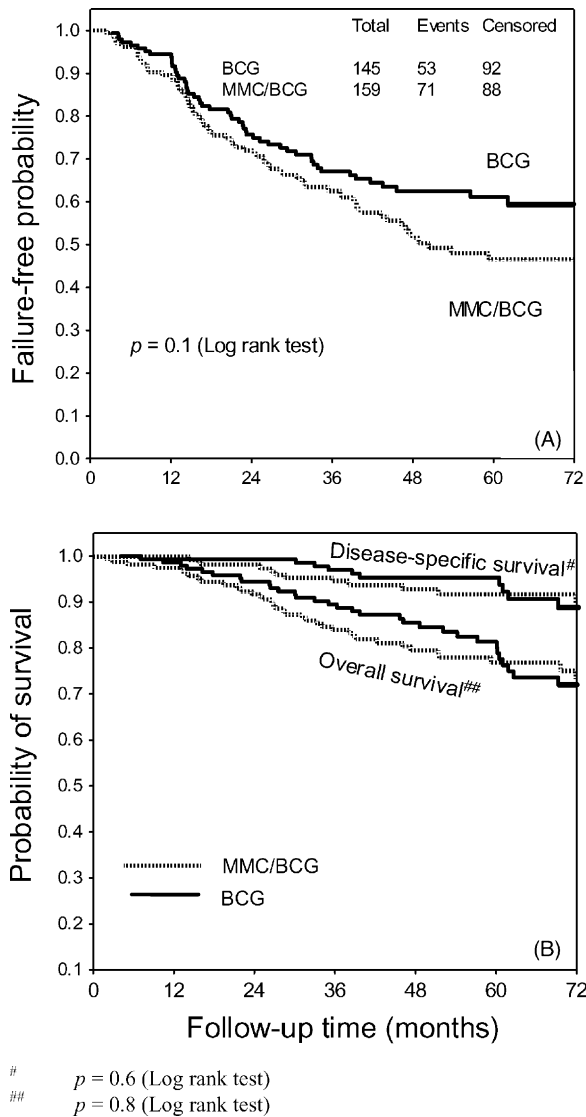


Fig. 4. (A) Failure-free estimates. (B) Estimates for overall (two lowermost plots in Fig. 4B) and bladder cancer-specific (two uppermost plots in Fig. 4B) survival in both treatment groups.

disease-free plots. However, with the level of failure-free curves at 15 months principally corresponding to the CR values at 12 months, the steady decline in the curves after 15 months illustrates that the remaining patients with early recurrence and an equal number of those without showed recurrence after one year. Half of these late recurrences were progressions.

3.5. Survival

Kaplan–Meier analysis of both cancer-specific and overall survival resulted in overlapping plots with no difference between the regimens (Fig. 4B). A total of 72 patients (23.7%) have died since the study began: 23 (7.6% of all patients) died of bladder carcinoma at the mean age of 75.0 years (95% CI, 71.9–78.1), 13

patients in the alternating group and 10 in the monotherapy group. The remaining 49 patients (15.8%) died of causes other than bladder carcinoma at the mean age of 79.1 (95% CI, 77.2–81.1).

3.6. Cox proportional hazards regression model

As expected from the Kaplan–Meier analysis, the primary end-points, disease-free interval and time to progression, were the only outcome variables that were significantly associated some explanatory variables.

3.6.1. Disease-free interval

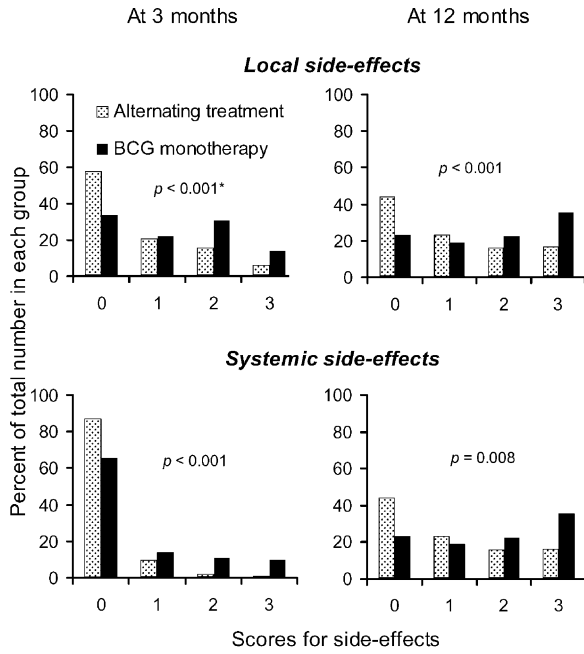
With explanatory variables analyzed separately, regimen, CIS category, and presence of previous irritative symptoms were significant predictors of recurrence. As in the Kaplan–Meier analysis, recurrence was most likely in patients with primary CIS and least likely in those with concomitant CIS. This was reflected in a significant hazard ratio between these two categories. In the multivariate model, a significant hazard ratio remained for regimen (ratio 1.4; 95% CI 1.0–2.0; $p = 0.03$) and between concomitant and primary CIS (ratio 1.6; 95% CI 1.1–2.5; $p = 0.02$), with these ratios representing the final values after including only the two variables in the model.

3.6.2. Time to progression

Because of the limited number of events, the results of this analysis should be interpreted with caution. Regardless of whether explanatory variables were analyzed separately or included simultaneously in the model, regimen had a tendency towards predicting progression, whereas the only significant hazard ratio was found between two CIS categories: The risk for progression was highest among patients with concomitant CIS and lowest among those with primary CIS (hazard ratio 2.4; 95% CI 1.1–5.2; $p = 0.02$). This was contrary to the results with time to recurrence and may be explained by the fact that the proportion of progressions as first events among recurrences was highest in those with concomitant CIS.

3.7. Side-effects

Compared with alternating therapy, patients treated with BCG monotherapy showed significantly higher scores for local and systemic side-effects at 3 months and 12 months (Fig. 5). In linear regression using several explanatory variables, also the presence of previous irritative symptoms and female gender were significant predictors of higher scores for local side-effects at 3 months and 12 months, in addition to BCG monotherapy. The most significant predictor of higher scores for local side-effects, BCG monotherapy, was



Scores for side-effects: 0 = none, 1 = not disturbing, 2 = disturbing, 3 = very disturbing
 Local side-effects included such symptoms as bladder irritation, bacterial or chemical cystitis, hematuria
 Systemic side-effects included such symptoms as malaise, fatigue, fever, flue-like symptoms
 * p-values are based on unpaired Student's test

Fig. 5. Percent distribution of scores for local and systemic side-effect at 3 months and 12 months.

the only significant predictor of higher scores for systemic side-effects.

Fig. 6 shows the probability of patients completing at least 14 of the 16 scheduled instillations. Objectively, alternating instillations were shown to be significantly

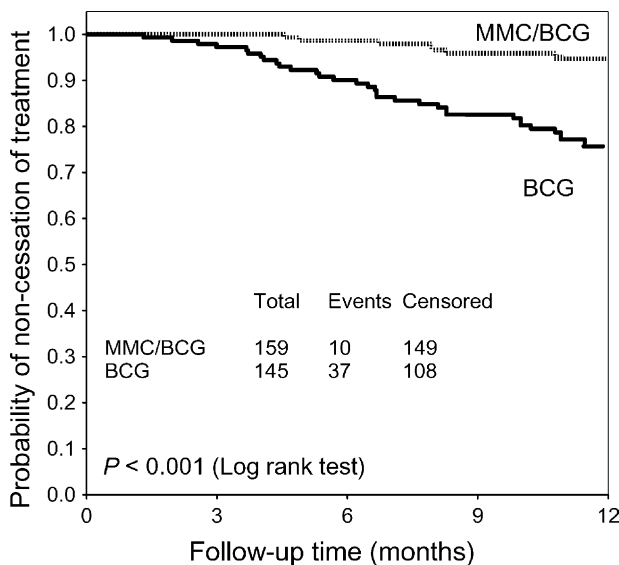


Fig. 6. Time to cessation of instillations because of side-effects.

better tolerated than BCG monotherapy ($p < 0.001$). Time to cessation was also analyzable with the Cox proportional hazards model, which identified the same significant predictors as did the linear regression of the local side-effects. With including only significant variables in the model, relative risk for cessation was 5.2 for BCG monotherapy/alternating therapy ($p < 0.001$), 2.9 for presence/absence of previous irritative symptoms ($p = 0.01$), and 2.2 for females/males ($p = 0.02$).

Despite the overall more favorable tolerability of the alternating therapy, no difference was evident among the most serious side-effects. Nine and five patients in the alternating group and monotherapy group developed contracted bladders, resulting in four cystectomies in each treatment group. There were no life-threatening systemic complications or deaths related to instillation therapy.

4. Discussion

The present series of 304 patients is hitherto the largest prospective study on patients with carcinoma in situ of the urinary bladder treated with intravesical instillations. We found BCG monotherapy to be significantly better than alternating instillation treatment with mitomycin C and BCG for reducing recurrence. We also noticed a tendency towards a higher risk for progression in the alternating group. However, with the number of cancer-specific deaths thus far low, we were unable to observe, between these two treatment groups, corresponding differences in survival. In addition to instillation regimen, CIS category seemed to dictate disease outcome.

A limited number of randomized, sufficiently large prospective studies compare BCG monotherapy with chemotherapy in superficial bladder carcinoma. Recently, two reports have appeared suggesting the overall superiority of BCG monotherapy over chemotherapy: Böhle et al. found, based on their “formal” meta-analysis, [11] BCG to be significantly better than MMC in reducing recurrence. This superiority was mainly attributed to BCG regimens involving maintenance for at least one year or 12 BCG instillations. Similarly, Sylvester et al. [13] found in their meta-analysis that BCG therapy comprising maintenance instillations significantly reduces the risk of progression as compared to no maintenance BCG therapy, to chemotherapy, or to immunotherapy other than BCG. Despite an obvious trend, neither of these meta-analyses with a notably short overall median follow-up could show a significant benefit of BCG maintenance in patients with CIS alone.

Apart from a tendency observed in one study, [21] no significant difference have been observed in single studies comparing BCG with MMC in patients with CIS alone. The only prospective trial demonstrating the superiority of BCG therapy over chemotherapy in patients with CIS is that by Lamm et al., who found BCG monotherapy to be superior to doxorubicin instillations [22]. However, as shown by the Bladder Cancer Clinical Guidelines Panel of the American Urological Association (AUA), doxorubicin is most likely inferior to MMC in reducing recurrence [12]. In contrast, the guidelines panel was unable to find any superiority of BCG over MMC as regards recurrence or progression. The panel therefore recommended, as recently as in 1999, either BCG or MMC for instillation treatment of CIS.

The time-point for initial assessment of response, whether by CR or Kaplan–Meier analysis, seems to vary considerably. Moreover, differences in endpoints and the method of censoring, or lacking information of censoring, make comparisons difficult. Nevertheless, the treatment arms of the present study attained or exceeded the reported average complete response rates or Kaplan–Meier disease-free estimates of approximately 70% at initial evaluation and 50% at five years [10]. Similarly, our initial CR for the BCG monotherapy group seems to be in agreement with that of the largest non-randomized trial on patients with CIS treated with short-term BCG therapy [23]. In contrast, comparison of our results with those of the second and third largest prospective randomized series reported by the South West Oncology Group (SWOG) [7,22] seems difficult because of considerable differences in the initial complete response rates (despite similar BCG induction therapy), method of censoring, and evaluation of long-term results.

The BCG instillation schedule of the earlier SWOG study [22] comprised six weekly instillations, followed by single instillations at 3, 6, 12, 18, and 24 months. Whereas the initial CR for patients with CIS was 70% at three months in the BCG monotherapy group, the long-term response was reported using only the Kaplan–Meier treatment failure-free estimate (different from ours). The estimate was approximately 80% at three months and 44.7% at five years. Because the initial CR was lower than was the failure-free estimate at three months, also the disease-free estimate at five years, if available, would be lower than the corresponding failure-free estimate.

In the more recent SWOG series [7], the better group was treated with a BCG maintenance schedule consisting of six weekly induction instillations, followed by three weekly booster instillations at 3, 6, 12, 18, 24,

30, and 36 months. This maintenance schedule seems to have gained a wide acceptance. For instance, the 2001 guidelines of the European Association of Urology [24] recommend it as a maintenance treatment for CIS. However, compared with most of other studies, the main disease-free analysis of that study involving patients with pTa-1 tumors with or without CIS is “biased”, with non-responders at three months (nearly 30% of randomized patients) excluded from the main analysis. To be comparable with the results of other studies, the disease-free survival estimates of the SWOG main analysis (100% at three months and approximately 60% at five years for the maintenance group) should be multiplied with a factor of 0.7. This results in substantially less impressive estimates, which, on the other hand, are unfavorably affected by considering deaths from any cause as events. As for pTa-1 patients with CIS in that study, the initial CR was as low as 55% at three months. Although many patients with persisting CIS at three months had CR after some booster cycles of BCG, producing an overall CR of 83.8%, no data is available on the duration of this CR.

Because of the better tolerability of alternating instillations in the present study, considerably more patients in the alternating group completed their instillations than did those in the BCG monotherapy group, but this was not translated into improved efficacy. Moreover, some cases with contracted bladder were caused by MMC instillations rather than by BCG. Indirectly, the superiority of BCG monotherapy over alternating therapy in the present study supports, in agreement with the two most recent meta-analysis, [11,13] the benefit of BCG maintenance immunotherapy over MMC chemotherapy.

The categorization of CIS in a European way into three subgroups is rarely seen in clinical studies. In the USA, CIS is categorized as asymptomatic focal primary disease, symptomatic diffuse primary disease, or disease associated with prior or concurrent stage Ta or T1 transitional cell carcinoma. Of these three US categories, the first is considered the least aggressive, and the second the most aggressive form [6]. The three categories in the present study had a tendency of behaving differently, with concomitant CIS appearing the most aggressive form of disease.

In the absence of an untreated control group, it is impossible to evaluate directly whether instillation therapy affected the natural course of the disease. Although we found no difference in death rates between treatment groups, our present progression rate of 17.8% is markedly lower than the reported natural rate of approximately 50% during five years [6]. On the

other hand, this rate is in agreement with the average rate of 13.9% reported in the recent meta-analysis, [13] bearing in mind that almost half of our progressions were T1 tumors (without muscle invasion), which we, with the definition of progression by others being most variable, [7,23,25] regarded as progression in the present study. Our readiness for cystectomies even for the cases with T1 recurrence may have contributed to our low and similar disease-specific death rates in both treatment arms. Our median follow-up is too short for drawing fundamental conclusions about survival, however, since progression may occur after a disease-free period of 10 years [14]. In our experience, conservative treatment of CIS with one-year BCG instillation therapy combined with careful follow-up, and when needed, with prompt cystectomy, compares well with results in the literature. Despite active treatment, patients still have, as based on our present death rates, an approximately 30% risk of dying of this disease.

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Appendix A

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