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Long-Term Intravesical Adjuvant Chemotherapy Further Reduces Recurrence Rate Compared with Short-Term Intravesical Chemotherapy and Short-Term Therapy with Bacillus Calmette-Guérin (BCG) in Patients with Non–Muscle-Invasive Bladder Carcinoma

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Abstract

Objective: We present a randomised, parallel group, multicentre phase 4 trial comparing short- and long-term chemoprophylaxis with Mitomycin C (MMC) with short-term immunoprophylaxis with Bacillus Calmette-Guérin (BCG) after transurethral resection of the bladder for non–muscle-invasive bladder carcinoma.

Methods: Four hundred ninety-five patients with intermediate- to high-risk non–muscle-invasive bladder cancer (recurrent and/or multifocal pTaG1, TaG2–3, and T1G1–3) were randomised to BCG RIVM 2×10^8 CFU weekly for 6 wk, MMC 20 mg weekly for 6 wk, or MMC 20 mg weekly for 6 wk followed by monthly instillations for 3 yr.

Results: The 3-yr recurrence-free rates were 65.5% (95%CI, 55.9–73.5%) for short-term BCG, and 68.6% (59.9–75.7%) for short-term MMC, whereas recurrence-free rates were significantly increased to 86.1% (77.9–91.4%) in patients with MMC long-term therapy (log-rank test, $p = 0.001$).

Conclusions: Long-term MMC significantly reduced the risk of tumour recurrence without enhanced toxicity compared with both short-term BCG and MMC in patients with intermediate- and high-risk non–muscle-invasive bladder carcinoma. Our data provide a rationale for maintenance intravesical chemotherapy in this population.

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1. Introduction

Of patients with non–muscle-invasive bladder cancer, 50–70% will develop tumour recurrence and up to 40% will progress. The cancer-related death rate is up to 36.1% [1]. Risk factors for tumour recurrence and/or progression are tumour focality, tumour size, prior recurrences, stage, grade, and concomitant carcinoma in situ (CIS) [2]. Other prognostic factors are the quality of the primary resection and the administration of adjuvant or prophylactic intravesical therapy [3–6]. Intravesical adjuvant therapy with Mitomycin C (MMC) or Bacillus Calmette-Guérin (BCG) after transurethral resection (TUR) is a standard therapy for patients with intermediate- or high-risk non–muscle-invasive transitional cell cancer of the bladder [4,7]. Although the clinical value of intravesical adjuvant therapy is well established, the optimal drug as well as the optimal regimen is still debated. A recent survey [8] has shown a wide variation in current practice for non–muscle-invasive bladder cancer.

Although, according to the guidelines of the European Association of Urology (EAU), the treatment for low-risk and high-risk tumours is well-defined, mitomycin and BCG are equally recommended for patients with intermediate-risk tumours. In contrast to these guidelines, recent meta-analyses [5,7,9,10] suggest an advantage of BCG therapy over MMC, even in intermediate-risk tumours. Despite this possible advantage of BCG, its use is limited by its side-effects, because 5–20% of patients will develop a BCG intolerance [11]. Another open question is the length of intravesical therapy. According to Bouffioux et al [12] a 12-mo course of intravesical chemotherapy does not yield better results than a 6-mo course, provided that an immediate postoperative instillation was administered. In contrast other authors [4,13,14] presented effective long-term intravesical chemotherapy regimens.

The aim of the current parallel group, randomised, open-label multicentre trial was to compare the effectiveness of long-term adjuvant therapy with MMC with short-term protocols using BCG or MMC in patients with primary intermediate- to high-risk (recurrent, multifocal or large [>3 cm] pTaG1 tumours, and pTaG2 tumours - small, solitary pT1G3) urothelial carcinoma.

2. Methods

2.1. Patients

Patients with primary transitional cell carcinoma of the bladder or patients with tumour recurrence after TUR without prior adjuvant therapy were eligible for trial participation if the histopathologic evaluation of their completely resected tumour revealed an intermediate-risk pTaG1 tumour (size >3 cm, recurrent, or multifocal tumour) or pTaG2 up to pT1 tumour (G1–3). Patients with a pT1G3 tumour were eligible in case of a unifocal small tumour (Ø ≤ 2.5 cm). Histopathologic evaluation was done according to the sixth edition of the *TNM Classification of Malignant Tumours* [15]. In cases of a pT1 tumour, all patients underwent a second transurethral resection of the bladder (TURB) 14–30 d after the first resection before randomisation.

Patients were not randomised in case of a muscle-invasive tumour or a concomitant CIS, evidence of lymph node or distant metastasis, or a pT1G3 tumour >2.5 cm. Other exclusion criteria were pregnancy, mental disease, reduced kidney function, or a second malignant disease.

All patients gave written informed consent. The study protocol was approved by the local ethical committee of the city of Hamburg and the institutional review board of the University Hospital Hamburg-Eppendorf.

2.2. Treatment and randomisation schedule

Randomisation was performed by use of a stratified permuted block randomisation scheme, balanced for treatment groups. Stratification was performed by hospital or private urologists. Patients were randomised to six weekly instillations of 20 mg MMC (MMC 6 wk), six weekly instillations of BCG RIVM (BCG 6 wk), or six weekly instillations of MMC 20 mg followed by monthly instillations of MMC 20 mg for 3 yr (MMC 3 yr). The theoretical number of instillations in the MMC long-term arm was 42 (six weekly instillations followed by monthly instillations for 36 mo). In case of recurrence, treatment was stopped. Instillation was performed with a volume of 20 ccm after emptying of the the bladder. Patients received 20 mg of MMC or RIVM 2×10^8 CFU, respectively. Patients were instructed to retain the instillation volume for at least 60 min but not longer than 120 min.

Adjuvant intravesical therapy was started 4 wk after TUR (after second TUR in case of a pT1 tumour). Prior to each instillation, haematuria was excluded by haemoglobin dipstick. Urinary tract infection was excluded by urine culture. In cases of haematuria or urinary tract infection, instillation was postponed for a week, with antibiotic treatment given if necessary.

2.3. Study end points

The primary efficacy parameter was recurrence-free interval, defined as the time span between date of randomisation and the date of histologically confirmed recurrence. Patients without recurrence were censored at the date of their last follow-up. Follow-up was performed with ultrasound of the upper urinary tract, urinary cytology, and cystoscopy every 3 mo in the first 2-yr and every 6 mo thereafter. Adverse events were documented throughout the study by the responsible physician.

2.4. Statistical analysis

Sample size was determined by assuming that a 10 percentage point ''increase in the recurrence free rate'' with MMC 3 yr

compared with MMC 6 wk and BCG 6 wk was worth detection. Five hundred thirty-one patients were planned to be enrolled in the full analysis set to give 80% power with a type I error of 5%.

Categoric data were presented in contingency tables with frequencies and percentages. Continuous data were summarised with median, first and third quartiles, and ranges. Recurrence-free interval was estimated by using Kaplan-Meier methods; comparisons were made using overall and pair-wise log-rank tests [16].

Two- and 3-yr recurrence-free rates were extracted from Kaplan-Meier curves. Cox proportional hazards models were applied to evaluate the treatment effect adjusted for other potentially relevant tumour-specific prognostic parameters. Incidences of adverse events were compared with the use of chi-square tests. All p values presented are two-sided.

Statistical analysis was based on the full analysis set, defined as all randomised patients analysed according to intention to treat. The statistical software system SAS, version 9.1.3, was used to perform the calculations.

3. Results

Between 1995 and 2002, 495 patients were randomised, with 179 patients randomised to receive MMC 6 wk, 153 to receive long-term MMC, and 163 to receive BCG. Demographics and disease characteristics of patients stratified by treatment arm are shown in Table 1.

In the MMC 6-wk arm all patients who started therapy received six instillations, except eight patients who discontinued prematurely. In the BCG arm, five patients did not receive the planned number of instillations.

In the MMC long-term arm. the median number of instillations in patients starting therapy was 21 (range: 1–45). Of these patients, 75% obtained up to 33 instillations, and 95.3% completed at least six instillations, whereas 53.5%, 36.2%, and 7.9% completed at least 1, 2, and 3 yr of maintenance therapy, respectively. In case of a tumour recurrence, the treatment was stopped and no further follow-up data were collected. Thus, looking only at those patients without relapse/death, we found the median number of instillations within the MMC long-term arm was 21 (interquartile range: 8–36).

Eleven percent of patients, equally distributed between treatment arms, were lost to follow-up. Discontinuation due to adverse events occurred in 1.8% of patients; none of the patients receiving 6-wk MMC instillation terminated the study prematurely for side-effects. In the BCG arm, three patients discontinued the study because of haematuria or dysuria. In the MMC long-term arm, study was terminated prematurely in eight patients because of haematuria and/or dysuria after a median number of 8 (range: 3–23) instillations.

The median follow-up time was 2.9 yr (range: 0–6.6 yr) and was equally distributed between treatment arms (overall log-rank test, $p = 0.39$). The overall incidence of recurrences was 20.8% ($n = 103$ of 495 patients). In the BCG 6-wk arm, 25.1% recurrences were observed compared with 25.7% in the MMC 6-wk arm and 10.4% in the MMC long-term arm. The 2- and 3-yr recurrence-free rates were 70.5%, and 68.6% for MMC 6-wk arm, 68.5% and 65.5% for BCG 6-wk arm, and 88.3%, and 86.1% for the MMC 3-yr arm, respectively. The log-rank test showed significant differences between treatment arms (log-rank test, $p = 0.001$). Pair-wise comparisons revealed MMC long-term arm to be superior to MMC 6-wk arm (log-rank test, $p = 0.0006$) and BCG (log-rank test, $p = 0.0005$). The Kaplan-Meier estimates are graphically presented in Fig. 1. Exploratory subgroup analyses underscored the advantage

Table 1 – Demographics, disease characteristics, and treatment courses

	Intermediate/high-risk patients		
	MMC 3 years ($n = 153$)	MMC 6 weeks ($n = 179$)	BCG 6 weeks ($n = 163$)
Sex (% males)	81.7%	78.8%	80.4%
Age (median [range])	67 (36–85)	68 (38–89)	67 (36–84)
Staging/grading			
TaG1	5.2%	15.1%	11.7%
TaG2	53.6%	54.2%	45.4%
TaG3	2.0%	2.2%	3.1%
T1G1	2.0%	2.8%	2.5%
T1G2	26.8%	22.4%	31.3%
T1G3	10.5%	3.4%	6.1%
Recurrent tumours	14.4%	15.6%	12.9%
Multifocal tumours	32.0%	42.5%	35.6%

MMC = Mitomycin C; BCG = Bacillus Calmette-Guérin.

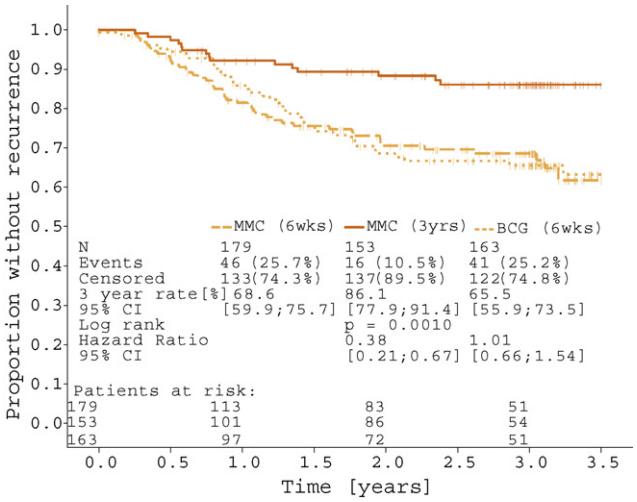

Fig. 1 – Kaplan Meier estimates for recurrence free interval.

of MMC long-term instillation irrespective of tumour histology. Within the large subgroup of 253 patients with pTaG2, the 3-yr recurrence-free rates were 74.0%, 70.0%, and 89.6% in the BCG 6-wk, MMC 6-wk and MMC long-term arms, respectively (log-rank test, $p = 0.0087$). Within the $n = 132$ pT1G2 patients, a descriptive superiority was detected, leading to 3-yr recurrence-free rates of 64.0%, 74.2%, and 81.1% within the BCG 6-wk, MMC 6-wk, and MMC long-term treatment arms, respectively (log-rank test, $p = 0.2915$). In patients with primary diagnosis of bladder carcinoma, a significant superiority of MMC-long-term treatment was detected (log-rank test, $p = 0.0134$) with associated 3-yr recurrence-free rates of 70.0% (BCG 6-wk), 70.4% (MMC 6 wk), and 85.4% (MMC long term). Analogous results were obtained in patients with recurrent tumours (log-rank test, $p = 0.0050$) leading to 3-yr recurrence-free rates of 26.4%, 59.3%, and 92.3%, respectively. Multivariate Cox proportional hazards modelling showed a hazard ratio of 0.38 (95% confidence interval [95%CI], 0.21; 0.69) for MMC long-term, and a hazard ratio of 1.09 (95%CI, 0.71; 1.68) for BCG 6 wk. These results coincided with the univariate analysis (Fig. 1) and underscore the validity of the results. The complete results of the Cox regression analysis are shown in Table 2.

Table 2 – Multivariate Cox regression analysis for recurrence-free interval

Factor	Hazard ratio	95%CI	*p* value
Treatment			
MMC (6 weeks)	1.0		
MMC (3 years)	0.38	[0.21; 0.69]	0.0012
BCG (6 weeks)	1.09	[0.71; 1.68]	0.6916
Tumour focality			0.074
Unifocal	1.0		
Multifocal	1.46	[0.96; 2.20]	
Primary/recurrent tumours			**0.0235**
Primary	1.0		
Recurrent	1.84	[1.09; 3.12]	
Tumour staging/grading			0.1084
pTaG1–2	1.0		
PTaG3	0.59	[0.14; 2.42]	
pT1G1–2	1.1	[0.70; 1.72]	
pT1G3	2.35	[1.13; 4.89]	

95%CI = 95% confidence interval; MMC = Mytomycin C; BCG = Bacillus Calmette-Guérin.

3.1. *Adverse events*

Analysing all patients with at least one documented instillation, dysuria was documented in 11.6%, 20.5%, and 17.3% of patients in MMC 6 wk, MMC 3 yr (long term), and BCG (6-wk), respectively. Haematuria was observed more often in patients in the MMC long-term arm (9.4%) and in the BCG arm (11.6%) than in those in the MMC 6-wk arm, in whom it was observed just once. Fever was seen more often in patients in the BCG arm (9.3%) than in patients receiving MMC 6-wk or long-term instillation (2.1%, and 2.4%, respectively). Discomfort was documented in 7.1% of patients in the MMC long-term arm compared with 4.1% in the MMC 6-wk arm and 4.7% in the BCG 6-wk arm. There was one case of a serious adverse event showing systemic tuberculosis with a granuloma infiltrating the arteria carotis externa, leading to a severe bleeding complication that required immediate vascular surgery. No patient experienced bladder shrinkage requiring urinary diversion.

4. Discussion

Although intravesical adjuvant or prophylactic treatment is well established and part of the routine in the clinical treatment of patients with non–muscle-invasive bladder cancer, the optimal treatment strategy is still under debate [7,10]. Recent meta-analyses [5,9,17] indicate an advantage of BCG over MMC regarding tumour recurrence and tumour progression. However, this advantage was most pronounced in patients undergoing long-term or maintenance BCG schedules. Another problem is that a subgroup analysis for pretreatment is not available in these studies. In a more recent meta-analysis, Huncharek et al [18] focused on this issue. They found that prior chemotherapy treatment in patients enrolled in a chemotherapy treatment

biased results in favour of BCG. Once the data were stratified on presence or absence of prior drug treatment, intravesical chemotherapy showed a 21–82% greater reduction in tumour recurrence at 1, 2, and 3 yr than did BCG. The authors therefore concluded that the perceived superiority of BCG immunotherapy could be an artefact of study design. Another problem with the mentioned meta-analyses is that a subgroup analysis for intermediate-risk papillary tumours is not possible. In the current study we compared the efficacy and tolerability of two 6-wk BCG and MMC treatment schedules with a maintenance MMC treatment arm in an intermediate- to high-risk population. None of the patients had received previous intravesical therapy. Patients with a muscle-invasive tumour or patients with a concomitant CIS were excluded.

In both 6-wk arms, similar recurrence rates were found. The 3-yr recurrence-free rates were 68.6% for MMC and 65.5% for BCG. This is an interesting finding, because it suggests an equal efficacy of MMC and BCG for papillary tumours in a short-term regimen. This finding was shown before for the comparison of two maintenance regimens. In an update of the Lundholm et al study [19] in which an overall superiority of BCG was described, Malmström et al [13] confirmed the overall superiority of BCG because of its better efficacy on nonpapillary tumours, but in the papillary subgroup, BCG and MMC had similar efficacy. These data are in contrast to the conclusions drawn in the meta-analyses of Bohle et al [5,17] and Sylvester et al [9] who described a superior efficacy of BCG over MMC.

In patients with high-risk bladder carcinoma, the superiority of BCG compared with intravesical chemotherapy is well accepted. Several authors favour BCG over MMC in high-risk non–muscle-invasive bladder cancer. Lundholm et al [19] showed a significant advantage for BCG regarding tumour recurrence in patients with high-risk superficial bladder, including CIS, pT1G3, and recurrent tumours. These results were confirmed by Lamm et al [20], who also found a significantly better recurrence-free survival in patients with recurrent bladder cancer. On the basis of these data, BCG has become the treatment of choice for grade 3 and high-risk bladder cancer [21,22].

It is debatable if this superiority can be transferred to patients with intermediate-risk tumours. Malmström et al [13] studied the effectiveness of BCG compared with mitomycin in a long-term protocol. Both treatments were carried out as long-term treatment for 2 yr. They found an overall statistical advantage regarding time to recurrence for the BCG treatment. But, interestingly, when focusing on papillary tumours versus nonpapillary tumours, they found a similar efficacy. However, it has to be considered that this subgroup consisted of only 167 patients. Witjes et al [23] found equal results when comparing a 5-mo trial of MMC with a 6-wk course of BCG. They also showed an advantage for MMC in patients without CIS. Krege et al [14] studied a population similar to ours, including primary pTa–pT1G1–3 tumours with a long-term MMC protocol compared with an intermediate-term (4-mo) BCG regimen and a TUR-only group. They found a lower risk of recurrence in the MMC group than in the BCG group.

We present data on a homogenous cohort of patients with primary tumours or nontreated recurrent Ta–pT1 papillary bladder cancer without concomitant CIS. It is noteworthy that, because of the health system in Hamburg, we have complete follow-up in the majority of patients with a low dropout rate. Both 6-wk arms achieved very similar recurrence rates. Our data underscore the equal effectiveness of MMC and BCG in papillary non–muscle-invasive bladder carcinoma for short-term regimens.

In contrast to both 6-wk arms, mitomycin long-term yielded a significantly lower recurrence rate and a significantly longer recurrence-free time interval. The multivariate Cox proportional hazards model underscored these results, leading to a risk reduction of 62% for a tumour recurrence compared with MMC standard therapy.

Adverse events were similar in all three arms, but patients receiving BCG had significantly more fever and haematuria. Severe adverse events including one case of systemic tuberculosis were reported in one patient.

Although BCG maintenance therapy is well accepted, this issue has not been finally clarified for chemoprophylaxis. According to Bouffioux et al [12], prophylaxis of longer than 6 mo is of limited benefit. In the current study, the MMC long-term protocol showed a statistically significant and relevant superiority regarding time to first recurrence. The recurrence-free interval was significantly higher in the MMC long-term protocol (86.1%). Our data prove that long-term prophylaxis with MMC achieves a significantly longer recurrence-free interval compared with 6-wk regimens, without the increased toxicity that is usually seen in BCG maintenance protocols [11].

Even if we could prove that a long-term course of chemoprophylaxis gains better results than a short-term protocol, it is not clear how long is long enough. Bouffioux et al [12] showed that maintenance instillation with chemotherapy for 12 mo did not

gain better results than a 6-mo course if an early instillation was administered. Consequently they found an advantage for a maintenance therapy if the first instillation was delayed. We used a 3-yr year protocol, whereas Malmström et al [13] and Krege et al [14] used a 2-yr protocol. With the 2-yr protocol, after a follow-up interval of approximately 5 yr, Malmström et al found an overall recurrence rate of 58%. In the BCG group, the recurrence rate was 53%, and it was 66% in the MMC arm. When focusing on papillary tumours, they found the recurrence rates were 66% (MMC) and 57% (BCG), respectively. Krege et al found recurrence rates of 26.8% (MMC), and 25.5% (BCG), respectively. Our data implicate that an instillation protocol longer than 12 mo results in an additional reduction in recurrence rates.

When investigating the quantity of instillations in the MMC long-term arm, we found that the median number of instillations was 21; however, only 7.9% received the full 3-yr instillation therapy. This finding means that the majority of patients did not receive the full treatment, indicating that an instillation protocol longer than 3 yr does not seem feasible. Another open issue is the dose of MMC, because Au et al [24] showed that the effectiveness of MMC is improved by a dose escalation. From the combination of data from Bouffioux et al [12], Sylvester et al [3], and Au et al [24], it has to be concluded that intravesical chemotherapy can be improved by early instillation, dose escalation, and extension of the instillation schedule. Although the optimal regimen of intravesical chemotherapy still has to be defined, it is obvious that current regimens can be improved by early instillation, application of a higher dose, and an instillation schedule of longer than 12 mo.

5. Conclusions

Long-term MMC significantly reduces the risk of tumour recurrence without enhanced toxicity, compared with both short-term BCG and MMC in patients with intermediate- and high-risk non–muscle-invasive bladder carcinoma. Our data provide a rationale for maintenance intravesical chemotherapy in this population.

Conflicts of interest

None of the authors will benefit financially from the publication of the manuscript.

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Editorial Comment on: Long-Term Intravesical Adjuvant Chemotherapy Further Reduces Recurrence Rate Compared with Short-Term Intravesical Chemotherapy and Short-Term Therapy with Bacillus Calmette-Guérin (BCG) in Patients with Non–Muscle-Invasive Bladder Cancer

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The optimal management of non–muscle-invasive, intermediate-risk bladder cancer remains in evolution. Dr. Martin Friedrich and colleagues present evidence that long-term mitomycin C (MMC) chemotherapy is superior to either short-term MMC or short-term bacillus Calmette-Guérin (BCG) in reducing the risk of tumor recurrence in patients with intermediate-risk and select high-risk non–muscle-invasive bladder cancer [1]. The study began in 1995 and was powered for 531 patients to detect a 10% increase in the recurrence-free rate with 3 yr MMC compared to the short-term regimens. A total of 495 patients were randomized, and the number of recurrences for short-term BCG and MMC and long-term MMC were 41 (25.2%), 46 (25.7%), and 16 (10.5%), respectively, and demonstrated statistical significance.

The authors are to be credited with this large phase 4 trial, but in all such trials that take 10 yr to complete and report, knowledge in the intervening time has changed. The practices of a single immediate intravesical chemotherapy instillation [2], maintenance BCG [3], and lower-dose BCG to minimize toxicity [4] are subsequently known to affect outcomes in these patients. Although this report supports the long-term use of MMC over short-term therapies, how long is still unclear. Although the long-term group should have received 42 treatments, the median received was only 21. It seems that patients receiving an early instillation may not benefit from longer than a 6-mo course as reported by Bouffioux [5], but longer than a 1-yr course may be in order if the initial instillation is delayed. The authors' take home message that "the current data show the effectiveness of intravesical chemoprophylaxis in intermediate- and high-risk carcinoma..." should be heeded carefully, because their high-risk group was limited to the least high-risk subset by excluding those with carcinoma in situ or T1G3 tumors >2 cm in size.

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