Bladder Cancer

Single Postoperative Instillation of Gemcitabine in Patients with Non-muscle-invasive Transitional Cell Carcinoma of the Bladder: A Randomised, Double-blind, Placebo-controlled Phase III Multicentre Study

Andreas Böhle a, Herbert Leyh b, Christian Frei b, Michael Kühn c, Reinhold Tschada d, Tobias Pottek e, Walter Wagner f, Helmut H. Knispel g, Wolfgang von Pokrzywnitzki h, Ferruh Zorlu i, Karin Helsberg i, Birgit Lübben j, Victoria Soldatenkova i, Clemens Stoffregen j, Hartwig Büttner j,* on behalf of the S274 Study Group

a Department of Urology, Helios Agnes Karll Hospital, Bad Schwartau, Germany (on behalf of the German AUO Trial Group)
b Department of Urology, Klinikum Garmisch-Partenkirchen, Garmisch-Partenkirchen, Germany
c Department of Urology, Johanniter Hospital, Stendal, Germany
d Department of Urology, Diakonissenkrankenhaus Mannheim, Mannheim, Germany
e Department of Urology, Klinikum Wedel, Wedel, Germany
f Department of Urology, Bundeswehrkrankenhaus Hamburg, Hamburg, Germany
gh Department of Urology, St. Hedwig Hospital, Berlin, Germany
i SSK Tepecik Research and Education Hospital, Yenisehir Izmir, Turkey
j Medical Department, Lilly Deutschland GmbH, Bad Homburg, Germany

Abstract

**Background:** Recurrence prophylaxis with intravesical gemcitabine (GEM) was effective and safe in patients with non-muscle-invasive bladder cancer (NMIBC); efficacy as single-shot instillation remains to be proved.

**Objective:** To compare the efficacy of a single GEM instillation versus placebo (PBO) immediately after transurethral resection (TUR) of tumour in patients with histologically confirmed NMIBC (pTa/pT1,G1–3).

**Design, setting, and participants:** This was a double-blind, randomised, PBO-controlled study in patients with clinical evidence of primary or recurrent NMIBC (Ta/T1,G1–3). Of 355 patients randomised at 24 urologic centres, 328 underwent TUR and received instillation (92.4%; GEM/PBO: 166/162). In case of non-malignancy, carcinoma in situ (CIS), ≥pT2 disease, or intraoperative complications, patients were discontinued.

**Intervention:** We used a single, postoperative 30–40-min instillation of GEM (2000 mg/100 ml of saline) or PBO (100 ml of saline) followed by continuous

* Corresponding author. Lilly Deutschland GmbH, Werner-Reimers-Straße 2-4, D-61352 Bad Homburg, Germany. Tel. +49 6172 273 2059; Fax: +49 6172 273 2520. E-mail address: buettnerh@lilly.com (H. Büttner).
bladder irrigation for ≥20 h. A second TUR (no instillation) and adjuvant bacillus Calmette-Guérin (BCG) instillations were allowed.

**Measurements:** Primary outcome was recurrence-free survival (RFS). Secondary outcomes included type of recurrence and adverse events. To detect a difference in RFS, 191 recurrences were required (80% power, log-rank test, \( \alpha = 0.050 \)).

**Results and limitations:** Two hundred forty-eight patients (69.9%, GEM, PBO: 124, 124) had histologically confirmed pTa/pT1 G1–3 Gx tumour and were eligible for efficacy (GEM: 76.6% male; median age: 65 yr; PBO: 83.1% male; median age: 67 yr). Treatment groups were balanced (pTa: 75.0%, 71.0%; G1–G2: 85.5%, 87.9%; recurrent tumour: 24.2%, 21.0%; BCG: 10.5%, 16.9%). After a median follow-up of 24 mo, there were only 94 recurrences and 11 deaths. The study was terminated early based on predefined decision criteria. RFS was high in both groups (12-mo RFS [95% confidence interval (CI)]: GEM: 77.7% [68.8–84.3]; PBO: 75.3% [66.3–82.3]). There was no significant group difference (hazard ratio [HR]: 0.946 [0.64–1.39], log-rank test, \( p = 0.777 \)).

**Conclusions:** In this study of NMIBC, the immediate single instillation of GEM 2000 mg/100 ml of saline after TUR was not superior to PBO in terms of RFS. Rigid continuous irrigation and improved TUR/cystoscopy techniques may have contributed to the high RFS in both groups.

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### 1. Introduction

At initial diagnosis, 70–80% of bladder cancers present as non-muscle-invasive tumours of stage pTa or pT1, with an indication for transurethral resection (TUR). Depending on tumour stage and grade, the number and size of lesions, and preceding recurrences, the probability of recurrence may be as high as 60% within 1 yr and 80% within 5 yr [1]. Up to 17% of tumours progress to muscle-invasive disease within 1 yr, and up to 45% of tumours progress to muscle-invasive disease within 5 yr [1].

According to a meta-analysis of patients with stage pTa/pT1 tumours, one single postoperative instillation of chemotherapy immediately after TUR decreased the risk of recurrence by 39% after a median follow-up of 3.4 yr [2]. Current guidelines of the European Association of Urology and the American Urological Association both recommend an immediate single instillation of chemotherapy after TUR for Ta/T1 tumours [3,4].

Further treatment after initial TUR/instillation depends on the risk of recurrence and progression to muscle-invasive disease [1]. Because residual tumours have frequently been detected after the initial TUR [5], a routine second TUR is currently considered for all patients with high-grade Ta or any T1 urothelial carcinoma [6]. Furthermore, patients with a high risk for recurrence and/or progression (eg, any high-grade Ta/T1, multifocal, or highly recurrent tumour) may receive adjuvant treatment with intravesical instillations of bacillus Calmette-Guérin (BCG) [3,7,8].

Classic agents used for single-dose intravesical chemotherapy include doxorubicin, epirubicin, and mitomycin C (MMC) [3]. Among newer agents, gemcitabine (GEM; 2’-2’-difluorodeoxycytidine) is well suited for intravesical instillation treatment [9] and is commonly used for systemic therapy of advanced invasive bladder cancer (BCa), mainly combined with cisplatin. Given systemically as a single agent, GEM yielded response rates of 23–28% [10,11]. Its molecular weight of 299 D is lower than that of MMC (389 D) or doxorubicin (589 D), which may enable GEM to penetrate the bladder mucosa with beneficial effects on early invasive bladder cancer (BCa). At the same time, its molecular weight is high enough to prevent significant systemic absorption in an intact bladder. In murine bladder models (MB 49), GEM prevented tumour cell implantation and resulting tumour outgrowth when given early (within 30 min) after coagulation of the bladder mucosa and instillation of tumour cell suspension [12]. In several phase I and phase II clinical studies, intravesical GEM was effective and safe at doses of 2000 mg in 50 or 100 ml of saline after TUR was not superior to PBO in terms of RFS. Rigid continuous irrigation and improved TUR/cystoscopy techniques may have contributed to the high RFS in both groups.

### 2. Materials and methods

#### 2.1. Study design

This was a randomised, double-blind, PBO-controlled multicentre study. The protocol was approved by institutional review boards. Patients were recruited between January 2004 and June 2005 at 24 urologic centres in...
Germany and Turkey. Written informed consent was obtained from each patient according to federal and local institutional guidelines. Patients with clinical evidence of primary or recurrent non-muscle-invasive bladder cancer (NMIBC; pTa/T1,G1–3) [20] were randomised to a single postoperative instillation of GEM or PBO. Randomisation was stratified by primary/recurrent disease and centre. If nonmalignancy, carcinoma in situ (CIS), or ≥pT2 disease was detected during TUR or by histopathology (or in the case of intraoperative complications), patients were discontinued but followed up for safety until month 3. Follow-up cystoscopies were scheduled at least at months 3 and 6 and every 6 mo thereafter. A second TUR (no instillation) and adjuvant BCG instillations were allowed.

2.2. Inclusion and exclusion criteria

Adult patients with clinical evidence of papillary, non-muscle-invasive transitional cell carcinoma of the bladder and indication for TUR (stage Ta/T1,G1–G3; no concomitant bladder CIS) were eligible if they met the following additional criteria: Karnofsky performance status >70%, adequate bone marrow reserve (white blood cells: ≥4 × 10^9/l; platelets: ≥140 × 10^9/l); haemoglobin: ≥10 g/dl, and adequate renal and hepatic function (serum creatinine: <2.0 mg/dl; bilirubin: <2.0 mg/dl); alanine transaminase and aspartate transaminase <2.5 times the upper limit of normal). Patients with weight loss >15% during the last 6 mo or prior chemotherapy within the last 6 mo, with more than three prior TURs, or with history of CIS were excluded.

2.3. Intravesical instillation

Patients received a single intravesical instillation of 2000 mg of GEM in 100 ml of saline (0.9% NaCl) or PBO (100 ml of saline). Study drug was instilled over 30–40 min immediately after TUR followed by continuous irrigation with saline for ≥20 h.

2.4. Objectives and outcomes

The primary objective of the study was to compare the efficacy of a single GEM instillation versus PBO in patients with histologically confirmed NMIBC (pTa/pT1,G1–1–3) [20], as measured by recurrence-free survival (RFS). RFS was defined as the time from randomisation to the date of the first procedure (biopsy, TUR) confirming histopathologic recurrence with or without disease progression (within the bladder) or death from any cause. Secondary outcomes included type of recurrence (NMIBC recurrence or progression to muscle-invasive tumour) and treatment-related adverse events within the first 3 mo after the instillation.

2.5. Sample size

The sample-size calculation was based on estimated 1-yr RFS rates of 63% for GEM and 50% for PBO based on earlier single-instillation studies with other agents [17–19]. One hundred ninety-one critical events (recurrence or death) were required to detect a difference in RFS (80% power, log-rank test, α = 0.05). A sample size of 328 patients with clinical evidence of NMIBC was needed to observe these 191 events within a 24-mo follow-up period, assuming 246 of these 328 patients would receive the instillation and have a histopathologic diagnosis of pTa/pT1 (G1–3/Gx).

2.6. Interim and final analysis

Unexpectedly, only 87 recurrences and 7 deaths were documented at the planned end of follow-up (minimum 24 mo). An interim analysis (approved by ethical review boards) was performed under the auspices of an assessment committee. Based on predefined stopping boundaries for the hazard ratio (HR) of RFS calculated according to Pampallona et al [21], the study was stopped early for futility reasons (HR < 0.629 for superiority, HR > 0.839 for futility; actual HR: 0.93). The final data set included all follow-up data until study termination (March 2008).

2.7. Analysis of recurrence-free survival

The distribution of RFS was estimated using the Kaplan-Meier method and compared by log-rank test. Patients were censored at baseline if the initial histopathology revealed nonmalignancy, CIS, muscle-invasive cancer, or any other indication for cystectomy. Subgroup analyses were performed by country, for patients with and without concomitant BCG treatment, with and without second TUR, newly diagnosed and recurrent NMIBC, with low-grade (G1/2) and high-grade (G3) NMIBC, and with single and multiple lesion tumours. A Cox proportional hazards regression model was used to estimate treatment group difference in RFS adjusted for stratification factors.

2.8. Safety analysis

All patients who received the single instillation of GEM or PBO were evaluated for safety. Adverse events were recorded up to month 3.

3. Results

Of 355 patients randomised, 328 (92.4%; GEM: 166; PBO: 162) underwent TUR and received the single instillation. Of these, 78 patients (23.8%; GEM: n = 40; PBO: n = 38) received an optional second TUR. Fig. 1 summarises patient disposition by treatment group. NMIBC of stage pTa/pT1,G1–3/Gx was histologically confirmed in 248 patients (GEM: n = 124; PBO: n = 124). These patients were eligible for efficacy (GEM: 76.6% male; median age: 65 yr; PBO: 83.1% male; median age: 67 yr). Patient characteristics were similar in both treatment groups (Table 1). Tumours varied from low to high risk, with 43.1% multiple-lesion (GEM: 47.6%; PBO: 38.7%) and 10.9% high-risk G3 tumours (GEM: 10.5%; PBO: 11.3%). Furthermore, 22.6% of patients had recurrent disease (GEM: 24.2%; PBO: 21.0%), with a median time since last recurrence of 1.1 yr (GEM: 1.2 yr; PBO: 1.1 yr; range: 0–16.1).

Compliance with protocol-defined instillation procedures was high: In the GEM group, the actual mean volume instilled was 98.8 ± 7.7 ml, and median duration of instillation was 35 min in both groups. Saline irrigation was performed in all but one patient (PBO group). The proportion of patients with irrigation time <20 h was low (GEM: 12.1%; PBO: 7.3%).

Compliant BCG was used in 34 (13.7%) of efficacy-eligible patients (GEM: 10.5%; PBO: 16.9%); 14 patients (5.6%; GEM: n = 5; PBO: n = 9) received more than six BCG instillations. Furthermore, six patients (2.4%), three each for GEM and PBO, received nonallowed other instillation treatment during the follow-up period (MMC: n = 5; doxorubicin: n = 1). Of these, two patients (GEM: n = 1; PBO: n = 1) experienced recurrences.

3.1. Recurrence-free survival

After a median follow-up of 23.6 mo (range: 0–46), there were only 94 recurrences (GEM: n = 48; PBO: n = 46) and 11
deaths (GEM: n = 4; PBO: n = 7). RFS was high in both treatment groups (Fig. 2); median RFS was 37.2 mo for GEM and 40.2 mo for PBO. There was no significant treatment group difference (HR: 0.946 [0.64–1.39], log-rank p = 0.777). The 12- and 24-mo RFS rates were 77.7% (95% confidence interval [CI]: 68.8–84.3) and 64.0% (95% CI: 54.1–72.3) for GEM versus 75.3% (95% CI: 66.3–82.3) and 60.7% (95% CI: 51.0–69.1) for PBO.

NMIBC recurrence rates and progression to muscle-invasive disease were also similar in both groups (Table 2). Of 94 recurrences (GEM: n = 48; PBO: n = 46), 89 (94.7%) were pTa/pT1 tumours (GEM: 91.7%; PBO: 97.8%). Prespecified, exploratory subgroup analyses did not reveal significant treatment group differences in patients with high- or low-risk tumours (G1/G2 vs G3), primary or recurrent disease, with or without optional second
TUR, or with or without concomitant BCG treatment (Table 3).

3.2. Treatment tolerability

All patients receiving the instillation (GEM: n = 166; PBO: n = 162) were followed up for safety until month 3. During this period, 29.5% of GEM and 26.5% of PBO group patients reported one adverse event or more. One PBO group patient died during this 3-mo period (septic shock unrelated to study drug or protocol procedure). Adverse events possibly related to instillation treatment were rare (GEM: 6.6% of patients; PBO: 3.7% of patients; all nonserious). The only possibly related adverse events reported more than once per group were alopecia (GEM: 1.2%; PBO: 0%), pyrexia (GEM: 1.2%; PBO: 0.6%), and procedural pain (GEM: 1.2%; PBO: 0%).

4. Discussion

In this PBO-controlled study of NMIBC, a single instillation of GEM 2000 mg/100 ml of saline immediately after TUR was not superior to PBO in terms of RFS. RFS was high in both treatment groups, with 12- and 24-mo rates of 77.7% and 64.0% for GEM versus 75.3% and 60.7% for PBO. These results were unexpected, particularly when considering the patients’ risk profiles: 43.1% had multiple lesions, 10.9% had G3 tumours, and 22.6% had recurrent disease. In earlier randomised studies of patients with similar or lower-risk NMIBC, single post-TUR instillations of doxorubicin or epirubicin had been superior over TUR alone or PBO. In 170 patients with single-lesion NMIBC <3 cm in diameter, RFS rates at 1, 2, and 3 yr for doxorubicin (instillation time 1 h) were 92.4%, 82.7%, and 78.8% versus 67.0%, 55.7%, and 52.6%, respectively, after TUR only (p = 0.0007) [17]. In a study of 200 patients with primary NMIBC, RFS rates after median 3-yr follow-up were 51% for epirubicin (100 mg/100 ml of saline, 2 h) versus 24% for TUR alone [19]. In 431 patients with single-lesion, primary, or recurrent NMIBC, RFS rates after 2-yr follow-up were 71% for epirubicin

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Table 1 – Characteristics of patients eligible for efficacy (N = 248)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>GEM (n = 124)</th>
<th>PBO (n = 124)</th>
<th>Total (N = 248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yr (range)</td>
<td>65 (24–89)</td>
<td>67 (39–87)</td>
<td>66 (24–89)</td>
</tr>
<tr>
<td>Gender: male, No. (%)</td>
<td>95 (76.6)</td>
<td>103 (83.1)</td>
<td>198 (79.8)</td>
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<tr>
<td>PS (Karnofski), No. (%)</td>
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<td></td>
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<tr>
<td>90–100%</td>
<td>114 (91.9)</td>
<td>117 (94.4)</td>
<td>231 (93.1)</td>
</tr>
<tr>
<td>80–85%</td>
<td>9 (7.3)</td>
<td>5 (4.0)</td>
<td>14 (5.6)</td>
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<tr>
<td>&lt;80%</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>1 (0.8)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Tumour type, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>94 (75.8)</td>
<td>98 (79.0)</td>
<td>192 (77.4)</td>
</tr>
<tr>
<td>Recurrent</td>
<td>30 (24.2)</td>
<td>26 (21.0)</td>
<td>56 (22.6)</td>
</tr>
<tr>
<td>No. of lesions, No. (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Solitary</td>
<td>61 (49.2)</td>
<td>71 (57.3)</td>
<td>132 (53.2)</td>
</tr>
<tr>
<td>Two lesions</td>
<td>32 (25.8)</td>
<td>20 (16.1)</td>
<td>52 (21.0)</td>
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<tr>
<td>Three or four lesions</td>
<td>21 (16.9)</td>
<td>21 (16.9)</td>
<td>42 (16.9)</td>
</tr>
<tr>
<td>Five or more lesions</td>
<td>6 (4.8)</td>
<td>7 (5.6)</td>
<td>13 (5.2)</td>
</tr>
<tr>
<td>No specific sites documented</td>
<td>4 (3.2)</td>
<td>5 (4.0)</td>
<td>9 (3.6)</td>
</tr>
<tr>
<td>Final histopathologic staging*, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pTa</td>
<td>93 (75.0)</td>
<td>88 (71.0)</td>
<td>181 (73.0)</td>
</tr>
<tr>
<td>pT1</td>
<td>31 (25.0)</td>
<td>36 (29.0)</td>
<td>67 (27.0)</td>
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<tr>
<td>Final histopathologic grading*, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>57 (46.0)</td>
<td>66 (53.2)</td>
<td>123 (49.6)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>49 (39.5)</td>
<td>43 (34.7)</td>
<td>92 (37.1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>13 (10.5)</td>
<td>14 (11.3)</td>
<td>27 (10.9)</td>
</tr>
<tr>
<td>Grade unknown (Gx)</td>
<td>5 (4.0)</td>
<td>1 (0.8)</td>
<td>6 (2.4)</td>
</tr>
</tbody>
</table>

GEM = gemcitabine; PBO = placebo; PS = performance status.

* Worst staging of initial and optional second transurethral resection.

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Fig. 2 – Kaplan-Meier plot of recurrence-free survival.*

CI = confidence interval; GEM = gemcitabine; PBO = placebo; HR = hazard ratio.

* Noneligible patients were censored at baseline.
(80 mg/50 ml of saline, 1 h, within 6 h after TUR) versus 59% after PBO [18]. In 219 patients with primary or recurrent G1/2 NMIBC, RFS rates after 3.9 yr of follow-up were 38% for epirubicin (80 mg/50 ml of saline, 1 h, within 24 h after TUR) versus 23% after TUR only [22]. One recent PBO-controlled study of epirubicin (50 mg/50 ml of saline, 1 h, within 6 h after TUR) in 307 evaluable patients found recurrence rates of 51.0% with epirubicin versus 62.5% with PBO after 2 yr (p = 0.04) [23].

Why were we unable to show corresponding superiority of the GEM single instillation over PBO? One explanation might relate to the mechanism of action: Although anthracyclines such as epirubicin or alkylating agents such as MMC are effective during all phases of the cell cycle, GEM is a pyrimidine analogue acting phase-specifically during DNA replication only. A single instillation of 30–40-min duration, as used in our study, might have been too short to catch all tumour cells during DNA replication. In cell culture systems, the effect of GEM on deoxynucleotide triphosphate pool depletion occurred during the first 30 min and reached the maximum effect within 2 h [24,25]. However, in mouse model experiments, GEM reached maximal inhibition of tumour cell growth after 30 min of instillation time; longer retention times had no additional effect [12].

For phase-specific agents such as GEM, repeated instillation schedules might be more appropriate, as supported by a small, open-label phase II study [26]. Patients were randomised to a single GEM instillation (2000 mg/100 ml of saline, 1 h; n = 11) or two GEM instillations per week for 3 wk (n = 11) or one GEM instillation per week for 6 wk (n = 10). After 9 wk, 10% of patients in the single-instillation group versus 40% and 44% in the multiple instillation groups were in complete remission, suggesting that only multiple dosing regimens were effective.

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Of note, some recent studies with other agents also failed to show superiority of single-dose instillations: In 161 high-risk patients, RFS rates after a median follow-up of 15.3 mo were 57.5% after early single-dose instillation of epirubicin (80 mg/50 ml of saline) followed by weekly adjuvant BCG treatment versus 50.6% with BCG alone [27]. However, this study may have been underpowered to detect realistic treatment group differences [28]. In 105 patients with

<table>
<thead>
<tr>
<th>Table 2 – Recurrences and progression during long-term follow-up, efficacy eligible patients (N = 248)</th>
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<tr>
<td>GEM (n = 124)</td>
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<tr>
<td>Any recurrence/progression of BCa*, No. (%)</td>
</tr>
<tr>
<td>Recurrence of NMIBC (pTa or pT1), No. (%)</td>
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<tr>
<td>Progression to muscle-invasive (≥pT2) disease, No. (%)</td>
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<td>pTmax, No. (%)</td>
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GEM = gemcitabine; PBO = placebo; BCa = bladder cancer; NMIBC = non-muscle-invasive bladder cancer.

* Histopathologically confirmed.

<table>
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<th>Table 3 – Exploratory analyses of recurrence-free survival in different patient subgroups, efficacy eligible patients (N = 248)</th>
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<td>Subgroup analysis</td>
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<td>By risk group</td>
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<td>Low risk (G1/G2)</td>
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<td>High risk (G3)</td>
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<td>By number of lesions</td>
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<td>Single lesion</td>
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<td>Multiple lesions</td>
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<td>Without BCG</td>
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<td>By country</td>
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<td>Germany</td>
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<td>Turkey</td>
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RFS = recurrence-free survival; GEM = gemcitabine; PBO = placebo; HR = hazard ratio; CI = confidence interval; TUR = transurethral resection; BCG = bacillus Calmette-Guérin.

* n = total number of patients in subgroup.
intermediate-risk tumours, NMIBC recurrence rates after a mean follow-up of 22.7 mo were 34.0% following single-dose instillation of MMC versus 46.2% for TUR only [29]. Our data were similar to the MMC group in both treatment arms, with recurrence rates for NMIBC without progression of 35.5% for GEM and 36.3% for PBO after a median follow-up of 23.6 mo (Table 2).

The most striking finding of our study was that RFS was high—75% after 1 yr—in the PBO group as well. One possible explanation may be that continuous irrigation with saline was required per protocol for at least 20 h. Most previous instillation studies did not predefine or report irrigation times. One previous randomised trial addressed this topic [30]. Eight hundred sixty-six patients with stage Ta/T1 NMIBC were randomised to either TUR alone or TUR followed by irrigation with glycine or saline for ≥18 h. Time to recurrence was prolonged in patients receiving the postoperative irrigation (HR: 0.83; 95% CI: 0.69–1.00; p = 0.05). Two-year RFS rates were 51% with irrigation versus 45% without irrigation. The authors concluded that postoperative irrigation was easy to give, had little or no toxicity, and showed evidence of a benefit in terms of reduction of recurrence.

Also, the quality of diagnostic and TUR techniques has improved during recent years, particularly by increasing use of photodynamic cystoscopy techniques and second (restaging) TURs [31,32]. Thus, incomplete resections or overlook of muscle-invasive disease should have decreased, possibly explaining the lower recurrence rates in recent studies, as in our study or the study by Jalón Monzon et al [29].

The single GEM instillation used in our study (2000 mg/100 ml of saline, 30–40 min) was well tolerated. The only possibly treatment-related adverse events reported for GEM more than once were alopecia, pyrexia, and procedural pain in two patients each. The two cases of alopecia are difficult to explain. In phase I pharmacokinetic studies, systemic absorption of intravesical GEM up to 40 mg/ml (2000 mg/50 ml), kept in the bladder for up to 2 h, was minimal and transient and thus unlikely to produce clinically significant adverse events [9,14,16]. Nevertheless, occurrence of unnoted bladder perforations and, therefore, higher systemic absorption of GEM cannot be excluded.

A possible limitation of our study is the short instillation time of 30–40 min we had chosen to minimise local toxicity and enhance feasibility. As discussed above, most previous instillation studies used instillation times of 1–2 h.

Concomitant BCG treatment was allowed, but subgroup analyses revealed no impact on the overall results (Table 3). Furthermore, few patients (2.4%) received nonallowed instillation treatment with MMC (n = 5) or doxorubicin (n = 1). However, patients and recurrences were equally distributed across treatment groups (three patients per group, one each had recurrence).

A major limitation is that we did not collect lesion sizes and thus were unable to provide subgroup analyses for low-, intermediate-, and high-risk NMIBC according to the European Organisation for Research and Treatment of Cancer (EORTC) risk classification [1]. Based on a recent epirubicin study in 219 patients with G1/G2 NMIBC, the authors had suggested that the benefit was minimal in intermediate- and high-risk patients [22]. However, our subgroup analyses in patients with low-grade (G1/2) and high-grade (G3) lesions and in patients with single and multiple lesion tumours revealed no statistically significant differences between GEM and PBO in any subgroup (Table 3), indicating that there was no treatment effect specific for high- or low-risk tumours. However, these subgroup analyses were exploratory, and the small sample size in some subgroups prohibits definitive conclusions.

5. Conclusions

In this study of NMIBC, the single instillation of GEM 2000 mg/100 ml of saline immediately after TUR was not superior to PBO in terms of RFS. Our data do not support the general use of GEM single-instillation treatment for all NMIBC patients irrespective of risk. Continuous saline irrigation (≥20 h) and improved TUR/cystoscopy techniques may have contributed to the high RFS rates in both groups. A 12-mo RFS of 75% with PBO should be considered for design of future instillation studies in similar patient populations.

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Study concept and design: Böhle, Büttner, Stoffregen.

Acquisition of data: Böhnle, Frei, Knispel, Kühn, Leyh, Pottek, Tscha da, von Pokrzywinitzki, Wagner, Zorlu.

Analysis and interpretation of data: Böhle, Büttner, Helsberg, Lüb ben, Soldatenkova.

Drafting of the manuscript: Böhle, Büttner, Stoffregen.

Critical revision of the manuscript for important intellectual content: Frei, Knispel, Kühn, Leyh, Lüb ben, Pottek, Tschada, von Pokruz wyinitzki, Soldatenkova, Stoffregen, Wagner, Zorlu.

Statistical analysis: Soldatenkova.

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