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Comparative analysis of recurrence rates between intravesical gemcitabine and bacillus Calmette–Guérin induction therapy following transurethral resection of bladder tumors in patients with intermediate- and high-risk bladder cancer: A retrospective multicenter study

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Purpose: This study investigated the efficacy of intravesical gemcitabine as an alternative to bacillus Calmette–Guérin (BCG) therapy.
Materials and Methods: Data were retrospectively collected across seven institutions from February 1999 to May 2023. Inclusion criteria included patients with intermediate- or high-risk non-muscle invasive bladder cancer (NMIBC) who underwent transurethral resection of bladder tumors (TURBT) and received at least four sessions of intravesical gemcitabine or BCG induction therapy. Patient characteristics, complete remission (CR), occurrence, and progression rates were compared.
Results: In total, 149 patients were included in this study (gemcitabine, 63; BCG, 86). No differences were apparent between the two groups in baseline characteristics, except for the follow-up period (gemcitabine, 9.2±5.9 months vs. BCG, 43.9±41.4 months, p<0.001). There were no consistent significant differences observed between the two groups in the 3-month (gemcitabine, 98.4% vs. BCG, 95.3%; p=0.848), 6-month (94.9% vs. 90.0%, respectively; p=0.793) and 1-year CR rates (84.2% vs. 83.3%, respectively; p=0.950). Also, there was no significant statistical difference in progression-free survival between the two groups (p=0.953). The occurrence rates of adverse events were similar between the groups (22.2% vs. 22.1%; p=0.989); however, the rate of Clavien–Dindo grade 2 or higher was significantly higher in the BCG group (1.6% vs. 16.3%, respectively; p<0.001).
Conclusions: Intravesical gemcitabine demonstrated efficacy comparable to BCG therapy for the first year in patients with intermediate- and high-risk NMIBC. However, long-term follow-up studies are warranted.

Keywords: Bladder neoplasms; Gemcitabine; *Mycobacterium bovis*

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INTRODUCTION

Non-muscle-invasive bladder cancer (NMIBC) is a prevalent malignancy characterized by its tendency to recur and progress [1]. Among patients with NMIBC, those patients classified with intermediate or high-risk cancer require more aggressive treatment strategies to mitigate the risk of disease recurrence and progression [2]. Currently, transurethral resection of bladder tumors (TURBT) followed by intravesical therapy with bacillus Calmette–Guérin (BCG) is the gold standard therapeutic approach in this patient cohort. Thus, BCG therapy has demonstrated efficacy in reducing recurrence rates [3].

However, the global medical community has faced persistent challenges due to the chronic shortage of BCG since the closure of the manufacturer's laboratory (Sanofi) in 2016 [4]. This compound scarcity has led to significant delays in the delivery of vital intravesical BCG therapy, with some patients experiencing waiting periods exceeding two months, particularly in Korean regions. This critical lapse in timely treatment raises concerns regarding its potential impact on patient outcomes and necessitates the exploration of viable alternative therapeutic options [4-6].

Intravesical gemcitabine therapy has recently emerged as a potential substitute for BCG treatment [7,8]. Intriguingly, this therapeutic approach has gained recognition, particularly in the context of insurance coverage changes that now extend intravesical gemcitabine therapy for up to one year since the regulatory revision of insurance standards in February 2022 in Korea. The concurrent shortage of BCG and expanded insurance coverage for gemcitabine have prompted a closer examination of its efficacy as an alternative treatment strategy for intermediate/high-risk patients with NMIBC in Korea [9].

The primary objective of this study was to assess the efficacy of intravesical gemcitabine as a potential alternative to BCG therapy in patients initially diagnosed with intermediate/high-risk NMIBC. By conducting a comprehensive investigation of clinical outcomes, recurrence rates, and safety profiles associated with gemcitabine therapy, we hope to provide critical insights into the feasibility and effectiveness of this alternative approach.

MATERIALS AND METHODS

Approval for this study was obtained from the Institutional Review Board (IRB) of Chung-Ang University Gwangmyeong Hospital (IRB number: 2304-076-038), and the same approval was obtained from each participating institution. Due to the retrospective nature of the study, patient-specific information was not included in the data collection process, and the requirement for patient written or verbal informed consent was waived.

This study was initiated as a research project by the Bladder Cancer Study Group of the Korean Urological Oncology Society, involving participation from seven institutions. Retrospective data collection was conducted across the institutions from February 1999 to May 2023.

Patients included in the study underwent TURBT following an initial diagnosis of bladder tumors and were categorized as intermediate/high-risk according to the American Urological Association (AUA) risk classification. The study included adults aged 18 years and older. The selection criteria encompassed patients who had undergone at least four sessions of intravesical gemcitabine or BCG induction therapy, and who were followed up for more than three months. Patients who had previously undergone TURBT for bladder cancer or received any other type of intravesical therapy were excluded from the study.

The therapeutic BCG injected into the bladder was Oncotice®, a live attenuated strain of *Mycobacterium bovis*, at a dose of 12.5 mg in 100 mL sterile saline, mixed and instilled. For gemcitabine, a dose of 2,000 mg per session was mixed in 50 mL sterile saline and instilled. Intravesical therapy commenced two weeks to one month after surgery, with both drugs administered for six sessions during the induction phase. Maintenance therapy for intravesical gemcitabine followed a 1-year protocol, given monthly for one year. The duration of BCG maintenance was determined by the primary physician based on the patient's risk, ranging from one to three years, administered once a week for three weeks at 3-, 6-, 12-, 18-, 24-, 30-, and 36-month intervals.

The following patient data were collected: institution, sex, age, height, weight, body mass index, underlying conditions (hypertension, diabetes, chronic obstructive pulmonary disease, myocardial infarction, coronary-vascular accident, coronary artery disease, end-stage renal disease, smoking status, pack-years of smoking), ASA (American Society of Anesthesiologists Physical Status Classification) score, date of first transurethral resection (1st TUR), initial T stage, tumor multiplicity, initial grade, initial carcinoma *in situ* (CIS), initial AUA risk class, type of immediate intravesical therapy, type of induction therapy, date of last follow-up, recurrence status, time to recurrence, date of second TURBT due to recurrence, recurrence T stage, recurrence multiplicity, recurrence grade, recurrence CIS, recurrence AUA risk class, and whether the patient underwent cystectomy, along with the date of cystectomy (if appropriate). Data were ana-

lyzed in July 2023.

Disease progression was defined as an increase in T stage, grade, or occurrence of CIS. Time to recurrence was defined as the time from the date of the 1st TUR to the date of the 2nd TUR. The definition of complete remission (CR) was calculated by taking patients followed up for a specific period (three months, six months, or one year) as the denominator and those who did not experience recurrence during that period as the numerator. The common standard protocol for follow-up observations at each hospital was as follows: intermediate-risk patients underwent cystoscopy at 3-month intervals for the first year after surgery, followed by 6-month intervals. High-risk patients underwent cystoscopy at 3-month intervals for the first two years after surgery, followed by 6-month intervals. Regardless of risk, abdominal computed tomography was performed annually for follow-up. General follow-up observations were conducted for five years.

The IBM SPSS Statistics software version 27.0 (IBM Co.) was used for all the statistical analyses. The comparison of the CR rates utilized a chi-square test. For the comparison of progression-free survival (PFS), Kaplan–Meier survival analysis and the log-rank test were employed. In Tables 1, 2, and 3, the comparison between the two groups was conducted using Student's t-test to compare means, and Fisher's exact test was employed for the comparison of two categorical variables. Statistical significance was set at $p<0.05$.

RESULTS

A comprehensive data assessment was conducted in a cohort of 149 patients who underwent intravesical induction therapy following TURBT. Among these patients, 63 received intravesical gemcitabine and 86 patients received BCG induction therapy (Table 1). The baseline characteristics of the two groups demonstrated no significant differences, except for the follow-up duration, which indicated a significant variation (gemcitabine, 9.2±5.9 months vs. BCG,

Table 1. Baseline characteristics

Variable	Gemcitabine induction (n=63)	BCG induction (n=86)	p-value
Age (y)	72.8±9.8	70.6±9.2	0.159
Sex			0.415
Male	51 (81.0)	75 (87.2)	
Female	12 (19.0)	11 (12.8)	
Follow-up (mo)	9.2±5.9	43.9±41.4	<0.001
BMI	23.8±2.8	24.5±3.4	0.162
HTN	39 (61.9)	45 (52.3)	0.318
DM	22 (34.9)	24 (27.9)	0.462
COPD	5 (7.9)	3 (3.5)	0.411
MI, CVA, coronary artery disease	6 (9.5)	17 (19.8)	0.139
ESRD (dialysis)	0 (0.0)	0 (0.0)	>0.999
Smoking			0.852
Current	12 (19.0)	15 (17.4)	
Former	18 (28.6)	25 (29.1)	
Never	33 (52.4)	46 (53.5)	
T stage			0.838
Ta	34 (54.0)	45 (52.3)	
T1	29 (46.0)	41 (47.7)	
Multiplicity	46 (73.0)	66 (76.7)	0.743
Grade			0.679
Low grade	15 (23.8)	23 (26.7)	
High grade	48 (76.2)	63 (73.3)	
Concurrent CIS	18 (28.6)	19 (22.1)	0.476
AUA risk class			0.687
Intermediate	22 (34.9)	34 (39.5)	
High	41 (65.1)	52 (60.5)	

Values are presented as mean±standard deviation or number (%).
BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CVA, cerebro-vascular accident; ESRD, end-stage renal disease; CIS, carcinoma *in situ*; AUA, American Urological Association.

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Table 2. Details of the intravesical therapy and side effects

Variable	Gemcitabine induction (n=63)	BCG induction (n=86)	p-value
Induction therapy			<0.001
Gemcitabine	63 (100.0)	0 (0.0)	
BCG	0 (0.0)	86 (100.0)	
Induction count			0.085
4	4 (6.3)	1 (1.2)	
5	2 (3.2)	5 (5.8)	
6	57 (90.5)	78 (90.7)	
8	0 (0.0)	2 (2.3)	
Maintanence therapy			<0.001
None	17 (27.0)	79 (91.9)	
Gemcitabine	45 (71.4)	0 (0.0)	
BCG	0 (0.0)	7 (8.1)	
Epirubicin	1 (1.6)	0 (0.0)	
Average maintanence count	4.0±3.9	0.4±1.6	<0.001
Intravesical therapy symptoms			0.086
None or not evaluated	49 (77.8)	67 (77.9)	
Dysuria, frequency, urgency	7 (11.1)	10 (11.6)	
Hematuria	0 (0.0)	3 (3.5)	
Suprapubic discomfort/pain	3 (4.8)	3 (3.5)	
Fever	1 (1.6)	1 (1.2)	
Urosepsis, systemic BCG infection	1 (1.6)	1 (1.2)	
Nausea, vomiting	1 (1.6)	0 (0.0)	
Dizziness, headache, fatigue	1 (1.6)	1 (1.2)	
Intravesical therapy Clavien–Dindo grade			<0.001
None or not evaluated	49 (77.8)	67 (77.9)	
Grade 1 (mild)	13 (20.6)	5 (5.8)	
Grade 2 (moderate)	1 (1.6)	13 (15.1)	
Grade 3 (need admission)	0 (0.0)	1 (1.2)	

Values are presented as number (%) or mean±standard deviation.
BCG, bacillus Calmette–Guérin.

43.9±41.4 months; p<0.001).

Details of intravesical therapy and its side effects are presented in Table 2. Induction therapy was administered in six sessions for over 90% of patients of both groups, and the sessions were conducted at weekly intervals (gemcitabine, 90.5%; BCG, 90.7%; p=0.085). Maintenance therapy was more frequently administered in the gemcitabine group (73.0% vs. 8.1%, respectively; p<0.001).

During the course of intravesical induction therapy, the incidence rates of adverse events were similar between the gemcitabine and BCG groups (22.2% vs. 22.1%, respectively; p=0.989). However, when considering the severity of those adverse events based on the Clavien–Dindo grading system, the BCG group experienced a significantly higher rate of grade 2 or higher events than the gemcitabine group (1.6% vs. 16.3%, respectively; p<0.001).

The treatment outcomes are illustrated in Table 3. The 3-month CR rates were comparable between the gemcitabine and BCG groups (98.4% vs. 95.3%, respectively; p=0.848). In addition, no consistent significant difference was observed between the gemcitabine and BCG groups in the 6-month CR rate (94.9% vs. 90.0%, respectively; p=0.793) and 1-year CR rate (84.2% vs. 83.3%, respectively; p=0.950) (Fig. 1). However, the rate of disease progression among patients who experienced recurrence was significantly higher in the gemcitabine group (60.0% vs. 15.9%; p<0.001), with no statistically significant difference in the rate of PFS between the gemcitabine and BCG groups, respectively (p=0.953; Fig. 2).

DISCUSSION

NMIBC accounts for approximately 75% of newly diagnosed bladder cancers and is predominantly characterized by tumors confined to the mucosa (Ta, CIS) or submucosa (T1) [10,11]. NMIBC has a relatively favorable prognosis as compared to muscle-invasive tumors; however, the disease course

Table 3. Treatment outcomes

Variable	Gemcitabine induction (n=63)	BCG induction (n=86)	p-value
Summarized data			
Any recur at follow-up	5 (7.9)	44 (51.2)	<0.001
Follow-up (mo)	9.2±5.9	43.9±41.4	<0.001
Time to recur (day)	204.4±100.0	655.9±625.1	0.117
Median (IQR)	173 (107–317.5)	461.5 (175–854)	
3-month CR rate	62/63 (98.4)	82/86 (95.3)	0.848
6-month CR rate	37/39 (94.9)	63/70 (90.0)	0.793
1-year CR rate	16/19 (84.2)	55/66 (83.3)	0.950
Progression percent	3/5 (60.0)	7/44 (15.9)	<0.001
Understage percent	2/5 (20.0)	15/44 (34.1)	0.060
Stage persist percent	0/5 (0.0)	22/44 (50.0)	<0.001
1st recurrence data			
T stage			0.044
pT1	1 (20.0)	14 (31.8)	
pT2	0 (0.0)	3 (6.8)	
pTa	3 (60.0)	19 (43.2)	
CIS only	1 (20.0)	0 (0.0)	
Multiplicity	3 (60.0)	30 (68.2)	0.869
Grade			0.305
Low grade	1 (20.0)	16 (36.4)	
High grade	4 (80.0)	20 (45.5)	
Concurrent CIS	2 (40.0)	6 (13.6)	0.134
AUA risk class			0.675
Intermediate	3 (60.0)	22 (50.0)	
High	2 (40.0)	22 (50.0)	
Cystectomy	0 (0.0)	6 (13.6)	0.384

Values are presented as number (%), mean±standard deviation, or median (IQR).
BCG, bacillus Calmette–Guérin; IQR, interquartile range; CR, complete remission; CIS, carcinoma *in situ*; AUA, American Urological Association.

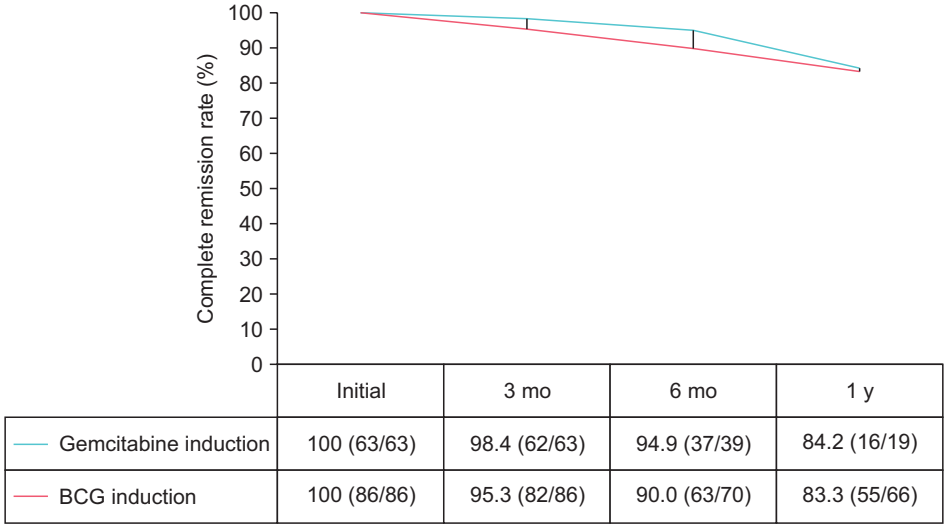

Fig. 1. One-year complete remission (CR) rate (%) comparison between intravesical bacillus Calmette–Guérin (BCG) and gemcitabine treatment. In patients with intermediate/high-risk non-muscle invasive bladder cancer, the initial 3-month, 6-month, and 1-year CR rates were similar for the intravesical BCG and gemcitabine groups (all p>0.05).

is marked by frequent recurrences, necessitating vigilant surveillance [12]. The current standard of care for NMIBC includes TURBT, followed by intravesical therapy, according to risk stratification. Given that residual tumors can be detected in 40%–45% of patients after TURBT, adjuvant intravesical therapy is important [13]. Intravesical instillation of BCG, an attenuated strain of *M. bovis*, has been the mainstay for preventing the recurrence and progression of

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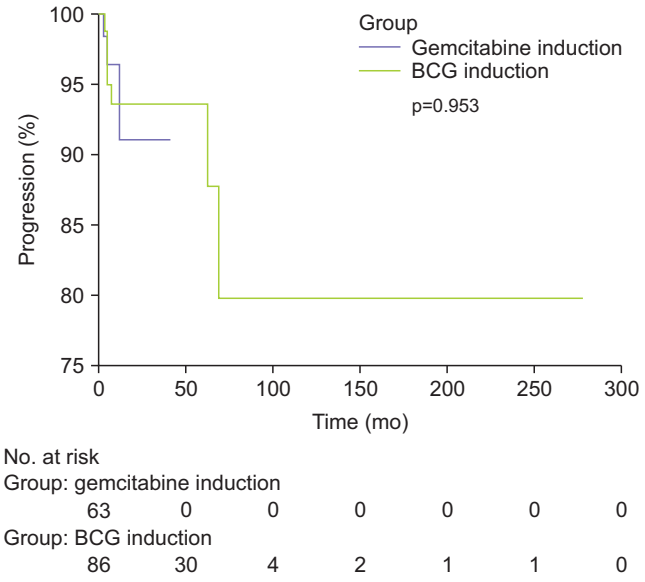

Fig. 2. Progression-free survival of intravesical bacillus Calmette–Guérin (BCG) and gemcitabine. There was no statistically significant difference in the progression-free rate between the intravesical BCG and gemcitabine treatment groups (p=0.953).

NMIBC for several decades [14-16]. However, intravesical BCG immunotherapy presents challenges, as this type of therapy can lead to local and systemic side effects. Global periodic shortages of BCG have also compromised treatment availability for patients [17,18]. Therefore, the exploration of alternative intravesical agents is imperative. Several studies revealed the inferiority of mitomycin C to BCG therapy, with its comparable recurrence risk yet reduced tolerability, manifested by increased allergic reactions and chemical cystitis [14,19]. Epirubicin, even though it exhibits less toxicity, remains less effective than BCG therapy in reducing recurrence [20].

Amid the chronic shortage of BCG, gemcitabine has emerged as a valuable intravesical chemotherapeutic agent. The extension of Korean health insurance coverage for intravesical gemcitabine therapy has amplified its use in first-line adjuvant intravesical settings since February 2022. This growing utilization of gemcitabine has underscored the need for further research on its role in the Korean population.

In this study, we retrospectively collected data from seven institutions to compare the efficacy and safety of intravesical gemcitabine and BCG in patients with intermediate- and high-risk NMIBC. Intravesical gemcitabine displayed a CR rate similar to that of BCG at three months after treatment. In addition, no consistent significant difference was observed between the two groups in the 6-month and 1-year CR rates. Despite accounting for a higher percentage of patients receiving maintenance therapy in the intravesical gemcitabine group as compared to the BCG group (gemcitabine, 71.4% vs. BCG, 8.1%), the long-term efficacy of intravesical gemcitabine appears to be favorable. This is an encouraging outcome considering the inclusion of a high proportion (65.1%, 41/63) of high-risk patients in the gemcitabine group. Prior research by Perera et al. [17] revealed recurrence rates of 53.1% and 28.1% (p=0.037) after intravesical gemcitabine and BCG treatments, respectively, in high-risk patients with superficial bladder cancer. In a systematic review, Shelley et al. [21] reported that intravesical gemcitabine therapy established comparable efficacy in intermediate-risk patients but decreased efficacy in high-risk patients. In this study, intravesical gemcitabine therapy demonstrated similar PFS to that of BCG (p=0.953). However, caution should be exercised when interpreting survival data because of the significant difference in the follow-up periods between the two groups.

Similar adverse effects were observed in the intravesical gemcitabine and BCG groups. Lower urinary symptoms including dysuria, frequency, and urgency were the most common adverse events in both groups. However, the intravesical BCG group exhibited more severe symptoms than the gemcitabine group; the rates of grade 1 and 2 symptoms were 20.6% and 1.6% for gemcitabine and 5.8% and 15.1% for BCG, respectively (p<0.001). The more tolerable toxicity profile of intravesical gemcitabine therapy aligns with previous studies [22,23].

Our retrospective analysis has several limitations. First, the small sample size may have rendered the results less robust. Second, over 90% of the patients in the intravesical BCG treatment group did not receive maintenance therapy, and this was attributed to the BCG shortage in Korea. In contrast, over 70% of the patients in the gemcitabine group underwent maintenance intravesical therapy. This procedural discrepancy was due to the retrospective design of this study, which may have caused the efficacy of intravesical BCG therapy to be considered unfavorable. Furthermore, there may be selection bias in the drug choices. Gemcitabine, known for fewer side effects, was implemented in a group with a higher average age and higher proportions of hypertension, diabetes mellitus, and chronic obstructive pulmonary disease in our study. Additionally, drug selection may have been influenced by issues related to the Korean drug supply. Although there was no statistical difference, these factors highlight the potential for selection bias in drug choices. Third, the follow-up period of the intravesical gemcitabine group was much shorter than that of the BCG group (9.2 months vs. 43.9 months, respectively; p<0.001). These differences in follow-up duration limited the estimation of long-term PFS. However, considering that intravesi-

cal gemcitabine treatment was initiated in February 2022, an approximate 9-month follow-up for the intravesical gemcitabine group was deemed acceptable.

CONCLUSIONS

In conclusion, intravesical gemcitabine exhibited efficacy similar to that of BCG as an induction therapy in patients with intermediate- and high-risk NMIBC for the first year. The occurrence rates of adverse events were comparable between the intravesical gemcitabine and BCG groups; however, mild adverse events were observed more frequently in the intravesical gemcitabine group. Gemcitabine could serve as a viable substitute in the short term, offering comparable efficacy to BCG in terms of early CR rates. However, long-term effects of over one year were not observed in this study; therefore, long-term follow-up studies are warranted. The findings from this study contribute to a deeper understanding of the role of intravesical gemcitabine as an alternative therapeutic approach for intermediate- and high-risk patients with NMIBC and may influence how healthcare professionals approach treatment decisions in this patient population.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Joongwon Choi, Byong Chang Jeong, and Jong Kil Nam. Data acquisition: Joongwon Choi, Kyung Hwan Kim, Hyung Suk Kim, Hyun Sik Yoon, Jung Hoon Kim, Jin Wook Kim, Yong Seong Lee, Se Young Choi, In Ho Chang, Young Hwii Ko, Wan Song, and Jong Kil Nam. Statistical analysis: Joongwon Choi and Jong Kil Nam. Data analysis and interpretation: In Ho Chang and Young Hwii Ko. Drafting of the manuscript: Joongwon Choi and Kyung Hwan Kim. Critical revision of the manuscript: Byong Chang Jeong and Jong Kil Nam. Administrative, technical, or material support: Hyung Suk Kim and Wan Song. Supervision: Byong Chang Jeong and Jong Kil Nam. Approval of the final manuscript: all authors.

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