RESEARCH ARTICLE

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Intravesical Gemcitabine for Non-Muscle Invasive Bladder Cancer after Bacillus Calmette-Guerin Treatment Failure: A Prospective Study

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Abstract

Backgrounds: The objective of this study was to assess the efficacy of gemcitabine as a treatment option for patients diagnosed with non-muscle invasive bladder cancer (NMIBC) who had previously experienced failure with Bacillus Calmette-Guerin (BCG) therapy in the last year. **Methods:** We prospectively enrolled 28 patients with recurrent NMIBC after previous intravesical treatment in the last year who declined or were unsuitable for cystectomy between 2021 and 2023. Gemcitabine at 2,000 mg/100 mL was instilled weekly for 6 weeks. Patients were assessed for response after 8 weeks, with subsequent evaluations scheduled every three months to one year. **Results:** The findings demonstrated that out of the 28 patients, 20 (71.4%) exhibited a complete response to intravesical gemcitabine treatment, and 8 (28.6%) had no complete response. The average age of the participants was 60.25 years. The study identified significant differences in treatment response based on age but without significant differences based on gender. Furthermore, there was no noteworthy association between tumor stage and grade and treatment response. Moreover, among patients with low-grade tumors, 66.7% achieved a complete response, while 72.7% reached a complete response among those with high-grade tumors. Of the patients who reached a complete response, 28.6% experienced no recurrence during one year of follow-up, and 42.9% developed recurrent disease within one year of treatment initiation. Ten months following treatment, a patient developed muscle-invasive bladder cancer and went on to cystectomy. **Conclusion:** In conclusion, the results suggest that intravesical gemcitabine could represent a feasible choice for NMIBC patients unresponsive to BCG therapy and ineligible for or unwilling to undergo cystectomy.

Keywords: Gemcitabine- cystectomy- NMIBC- BCG

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Introduction

Malignant bladder neoplasms are prevalent worldwide and represent a common type of neoplasm in the urinary system [1]. In men, this disease is the fourth most prevalent cancer, with a 4.3 times higher incidence compared to women. The prevalence of this disease is increasing in some developing countries and Eastern Europe. In Iran, various studies have indicated a rising prevalence of this disease [2, 3].

Approximately 75 to 85% of malignant bladder neoplasms are limited to the superficial layers of the bladder, referred to as non-muscle invasive bladder cancer (NMIBC). The treatment of non-muscle invasive carcinomas poses inherent challenges for physicians [4]. Patients with a high to moderate risk of cancer recurrence typically undergo treatment with transurethral resection and intravesical instillation of Bacillus Calmette-Guerin (BCG) with or without maintenance therapy [5]. BCG intravesical treatment is one of the most frequently used chemotherapeutic agents for treating NMIBC, with around one-third of patients experiencing mild urinary irritation as a side effect [6].

A six-week course of BCG therapy, followed by maintenance therapy, leads to a 30 to 40% reduction in the likelihood of recurrence [7]. However, up to 20% of patients are unable to tolerate this treatment, and an additional 20 to 40% do not respond to it, experiencing disease recurrence after resuming treatment. These instances represent treatment failure with BCG [6]. The cystectomy is the standard approach for the non-muscle invasive bladder cancer after Bacillus Calmette-Guerin treatment failure. If the patient does not have a good medical condition or refuse the surgery, next-line

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treatments such as intravesical chemotherapy are used [8].

As a deoxycytidine analog, gemcitabine exhibits a broad spectrum of antineoplastic activities, making it a valuable option for treating metastatic transitional cell carcinoma (MTCC), with a 22.5 to 28% response rate. This drug acts as an antimetabolite and a pyrimidine analog [7, 9]. It operates explicitly in the S phase of the cell cycle, inhibiting DNA synthesis in tissues upon activation. This drug is mistakenly incorporated into the DNA structure during DNA synthesis instead of cytidine nucleosides [10]. As it does not pair with other nucleosides, it disrupts DNA replication. Gemcitabine is well-tolerated and serves as a first- and second-line monotherapy for metastatic transitional cell carcinoma, with a treatment response ranging from 5.22% to 28% [11].

This study aims to improve the outcomes of patients with NMIBC who have shown no response to BCG by investigating the impact of gemcitabine on their treatment.

Materials and Methods

In this single-arm prospective cohort study, patients diagnosed with non-muscle invasive bladder cancer (NMIBC) who had experienced a recurrence within the past year following BCG therapy and were considered ineligible for or declined cystectomy due to their physical conditions were enrolled. The inclusion criteria consisted of the following: being over 18 years old, having a history of BCG treatment and recurrence within the past year, having a performance status (PS) of 0-1 according to the ECOG (Eastern Cooperative Oncology Group) criteria, being ineligible for cystectomy or unwilling to undergo the procedure, and specific laboratory values before treatment initiation (PLT >150,000 103/mm3, WBC >3,000 103/µL, AST, ALT less than 2 × normal, Total Bilirubin less than 1.5 × normal). The exclusion criteria included patient dissatisfaction with the treatment, being a candidate for and consenting to cystectomy, previous pelvic radiation, upper urinary tract infection, and gross hematuria.

The study enrolled 28 patients based on the specified inclusion and exclusion criteria. A urology specialist referred them from Hashemi Nejad Hospital to the oncology center at Firoozgar Hospital (Tehran, Iran) between August 2021 and December 2022. At the oncology center, the patients were scheduled to receive intravesical injections of gemcitabine (2g + 100 cc normal saline) via a Foley catheter every week for six weeks, with a 90-minute dwell time, followed by voiding. Premedication is generally not required for the intravesical injection .Cystoscopy was performed on all patients six weeks after completing the treatment. Patients who showed no evidence of tumor presence during the first cystoscopy were considered to have achieved a complete response and were subsequently scheduled for cystoscopy every three months for up to a year. Patients who presented evidence of tumor during the initial cystoscopy underwent a transurethral resection of bladder tumor, and their response to treatment was categorized as without a complete response, leading to their exclusion from the study.

Laboratory tests were performed at three distinct time intervals: prior to treatment initiation, after the third injection, and at the end of the treatment: AST, ALT, Bilirubin, ALP, CBC, BUN, Cr. In addition to laboratory tests, patients were assessed for tumor recurrence within one year following gemcitabine treatment, the necessity of cystectomy within one year of treatment initiation, and their response to the initial biopsy, which took place six weeks after the treatment. Side effects associated with gemcitabine injection were also documented. In SPSS software, Chi-Square was used for qualitative data, and the Fisher test was performed if necessary. We performed logistic regression analysis to check the association of the effect size of variables on the response and adjust other variables to the response to treatment. In multiple logistic regression analysis, all three variables, disease stage (T stage), tumor differentiation (Grade), and patient age, were analyzed to predict response to treatment.

Results

Twenty-eight patients with NMIBC and BCG failure patients, including 23 men and five women, were assessed. The median age was 60.25 years, ranging from 39 to 78 years. Among the 28 patients who received intravesical gemcitabine injections, 20 patients (71.4%) achieved a complete response, 8 patients (28.6%) were without complete response (3 patients with disease progression, 5 patients were in the same stage and grade before treatment) during the initial cystoscopy following the completion of the injections. In the initial cystoscopy after administering injections, 23 male patients were included in the analysis. Among them, 15 patients (65.2%) were classified in the complete response group, and 8 patients (28.6%) were without complete response. Additionally, all five female patients achieved a complete response. The Fisher test results indicated no statistically significant association between gender and treatment response ($p = 0.2$). 14 patients (50%) were included in the less than 60 years group, 13(93%) of them reached a complete response, and others were greater than 60 years, with 7 patients (50%) in the complete response group ($p= 0.03$).

Out of the 28 patients enrolled in this study, 16 patients (57%) were diagnosed with Ta, and 12 patients (43%) had T1, Ta+ CIS, and T1+ CIS. Complete responses were reported in 56.3% and 92% of patients, respectively ($p= 0.1$). For patients with low-grade tumors, 4 patients (66.7%) were included in the complete response group, and 2 (33.3%) belonged to the without complete response group. Similarly, for patients with High-Grade tumors, 16 patients (72.7%) were allocated to the complete response group, 6 (27.3%) belonged to the without complete response group. Among the 22 patients (79%) with a single lesion, 16 patients (72.7%) reached a complete response, 6 patients (27.3%) belonged to the without complete response group ($p= 0.5$). In the case of the 6 patients (21%) with two lesions, 4 patients (66.7%) belonged to the complete response group, and 2 patients (33.3%) belonged to the without complete response group. Out of the 11 patients (40%) who received a single injection of the prior therapy (BCG), 9 patients (82%) were in the complete response group, while 2 patients (18%) were in the without complete response group. Out of 17 (60%)

Table 1. Demographic and Clinical Information According Response

Variable	Number/percentage	Complete response	Without Complete response
Gender			
Male	23 (82.1%)	15 (65.2%)	8 (34.8%)
Female	5 (17.9%)	5 (100%)	-
T Stage			
Ta	16 (57%)	9 (56.3%)	7 (43.7%)
T1// Ta+ CIS// T1+ CIS	12 (43%)	11 (92%)	1 (8%)
Grade			
Low grade	6 (21.4%)	4 (66.7%)	2 (33.3%)
High grade	22 (78.6%)	16 (72.7%)	6 (27.3%)
Number of lesion			
One	22 (79%)	16 (72.7%)	6 (27.3%)
Two and more	6 (21%)	4 (66.7%)	2 (33.3%)
Prior therapy			
BCG×1	11 (40%)	9 (82%)	2 (18%)
BCG×2, ×3, BCG + Mitomycin	17 (43%)	11 (64.7%)	6 (35.29%)
Age(years)			
≤60	14 (50%)	13(93%)	1 (7%)
>60	14 (50%)	7(50%)	7 (50%)

who received multiple injections of BCG and BCG+ Mitomycin, 11 patients (64.7%) were categorized as part of the complete response group, while the remaining 6 patients (35.2%) were classified in the without complete response group. The results of the Chi-square test for these variables indicate that there is no statistically significant association between tumor grade (p=1), the number of lesions (p=1), and the number of BCG injections and treatment response (p=0.5) (Table 1).

We performed univariate logistic analysis to evaluate the effect of pre-therapy factors on response. Pre-therapy variables analyzed included age (≤60 vs >60), grade before therapy (high grade vs low grade), T stage (Ta vs T1, Ta+ CIS, T1+ CIS), number of previous courses of intravesical BCG/ BCG + Mitomycin (1 vs > 1), and number of lesions (1 vs > 1). There was a significant association between age and response (p=0.02). Regarding other variables, no significant predictors of response were identified (Table 2). All three variables of disease stage (T stage), tumor differentiation (Grade), and age of patients were analyzed in multiple logistic regression analysis to predict response to treatment. This analysis showed that the chance ratio of response to therapy in the age > 60 compared to ≤60 is 0.04 and significant (p= 0.02). Also, regarding the tumor stage in the T1 group, T+CIS, the response to treatment is 16 times more than the Ta group and is significant (p= 0.04) (Table 3).

Table 2. Univariate Logistic Regression: Predictors of Response to Gemcitabine

	OR(95% CI)	P-Value
Age		
> 60	0.077(0.008-0.758)	0.02
≤60 (Ref)	-	
T stage		
T1,Ta+CIS,T1+CIS	8.55(0.88-83.05)	0.06
Ta(Ref)	-	
Grade		
High	1.33(0.19-9.27)	0.7
Low(Ref)	-	
Number of lesion		
Multiple	0.75(0.108-5.216)	0.7
Single(Ref)	-	
BCG		
BCG×2,×3,BCG+Mitomycin	0.40(0.066-2.53)	0.3
BCG×1(Ref)	-	

Among the 20 patients (71%) who attained complete response in the initial biopsy following the injections, 28.6% remained free from disease recurrence during the one-year follow-up period. Out of the people who relapsed, 8 of them were Ta,3 were T1, and one patient had muscle-invasive bladder cancer. Patients tolerated gemcitabine injection well. Nine patients (32%) had grade 1 and 2 urinary complications. 3 patients (11%) experienced hematuria grade 1(according to CTCEA

Table 3. Factors Predicting Response to Treatment based on Multivariable Analysis

Variable	OR(95% CI)	P Value
Grade		
High	1.025 (0.062-16.99)	0.98
Low(Ref)	-	
T stage		
T1/T+ CIS	16.34 (1.08-264.94)	0.04
Ta (Ref)	-	
Age		
> 60	0.043 (0.003-0.61)	0.02
≤60 (Ref)	-	

version 5).

Discussion

The aim of this study was to examine the effectiveness of intravesical gemcitabine in the treatment of recurrent non-muscle invasive bladder cancer. Our study showed a complete response in 20 patients (71.4%) during the initial cystoscopy after the completion of injections. Conversely, eight patients (28.6%) were in the group without a complete response (3 patients with disease progression, 5 patients were in the same stage and grade before treatment).

82.1 % of patients were male, and 57% were T1. No significant difference was demonstrated in gender, grade, or T stage. 28.6% of patients had no disease recurrence during one year of follow-up, and one required cystectomy. In accordance with the findings of our study, Dalbagni et al. showed by examining 30 patients that 50% reached a complete response [7]. Sternberg et al. showed that 39% achieved complete response, and 80% had no disease progression within five years [12]. According to Rodolfo et al.'s study with 36 patients, disease-free survival after the end of induction treatment was 68% [13]. The phase 2 study SWOG S0353, which involved 47 patients, has shown that 47% of the patients achieved a complete response in the initial study after completing the gemcitabine injection, and 28% were disease-free after 12 months. 21% of patients did not experience relapse two years after starting treatment [10]. In the phase 2 study by Dalbagni et al. with 30 patients, 85% of the patients who achieved a complete response in the first cystoscopy relapsed within four months, and 11 patients (37%) of all participating patients underwent radical cystectomy at the end of one year from the end of the treatment [7]. Gunelli et al. [14] examined 40 patients and showed that 95% had a negative cystoscopy six months after the end of the treatment, 36% of them had a recurrence during the two-year follow-up, and only two patients underwent cystectomy during the 28-month follow-up [14]. The diversity of the reported results between different studies is due to the differences in the characteristics of patients and tumors, the dose of gemcitabine, the number of weeks of injection, and the existence of maintenance treatment in some studies.

Also, the frequency of grade 1 and 2 urinary complications was 32.2%, grade 1 hematuria 10.7%, and 57.1 % of patients were without complications. Contrary to the results of our study, Sternberg et al. revealed that 12% of patients had grade 3 complications, including skin rash, clots in deep veins, urinary symptoms, thrombocytopenia, and infection that required treatment discontinuation, and 42 % of patients without complications [12]. The percentage and the severity of side effects in this study, which had a twice-weekly injection protocol, were higher than the results of our study. The study by Zeng et al. showed that 60.6% of the patients tolerated completing the treatment without complications. The percentage of Dysuria, Fatigue/myalgia, and urgency/frequency was 18.2%, 15.2%, and 6.1%, respectively [15].

In the study of Dalbagni et al., grade 2 and 3 urinary complications were observed in 20% of patients. 6% of patients had grade 2 and 3 skin complications [7]. In Rodolfo et al.'s study, 35% of patients had grade 1 or 2 urinary complications, and 2% had grade 3 hematuria complications. 13% of patients had low-grade fever, and 15% had high-grade fever>38.5. Unlike our study, this study also administered maintenance treatment to the patients [13]. The studies have shown minimal systemic absorption of gemcitabine, along with favorable tolerance and minimal local and systemic adverse effects [16, 17].

We have done the multiple logistic regression analysis to predict the association between pre-treatment variables and group response. The results showed that the chance ratio of response to treatment in the age group over 60 compared to under 60 is 0.04, which is significant. Also, in the case of the T1, T+CIS group tumor stage, the response to treatment is 16 times higher than Ta and significant. Also, in the high-grade group compared to the low-grade group, the chance ratio of the response is 1.02, which is not significant. The study of Patrick et al. showed no significant relationship between gender, tumor grade, and response rate to gemcitabine and mitomycin combination therapy in patients [18].

Our study had strengths and weaknesses. It is one of the first studies conducted in Iran, and the promising results obtained can help other studies. One of the limitations of this study was the sample size. Therefore, studies involving a large number of participants may provide more meaningful data to compare the evaluated treatment methods. On the other hand, the limitation was the lack of long-term patient follow-up and maintenance treatment. According to the diversity of the reported results, doing more studies with various drugs and injection protocols can help the physician choose the best treatment.

In conclusion, our research findings suggest that intravesical gemcitabine may present a beneficial choice for individuals diagnosed with bladder cancer who have not responded to BCG therapy.

Author Contribution Statement

Concept and design: A.M.A.; acquisition of data: E.M.; analysis and interpretation of data: E.M.; drafting of the manuscript: E.M.; critical revision of the manuscript for important intellectual content: K.N. and A.A.; statistical analysis: A.A.

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Ethical approval statement and Consent to Participate

The protocol of the study was approved by the Ethics Committee of Iran University of Medical Sciences, Iran (IR.IMUS.FMD.REC.1400.611); a written informed consent form was also obtained from the patients or their legal guardian.

Clinical trial registration number

Not applicable.

Data availability statement

All data generated and analyzed during this study can be accessed through direct communication with the corresponding author and the agreement of all research team members.

Conflict of interest statement

The authors report no conflicts of interest.

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