Salvage therapy for BCG failure with intravesical sequential gemcitabine and docetaxel in patients with recurrent NMIBC

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ABSTRACT

Introduction: Bacillus Calmette-Guérin (BCG) failure occurs in approximately 40% of patients with non-muscle-invasive bladder cancer (NMIBC) within two years. We describe our institutional experience with sequential intravesical gemcitabine and docetaxel (gem/doce) as salvage therapy post- BCG failure in patients who were not candidates for or declined radical cystectomy (RC).

Methods: We retrospectively reviewed BCG-failure patients with NMIBC who received gem/doce from April 2019 through October 2022 at the CHU de Québec–Université Laval. Patients received at least five weekly intravesical instillations according to published protocols. Patients who responded to gem/doce had maintenance instillations monthly for up to two years. Primary outcome was progression-free survival (PFS). Secondary outcomes included recurrence-free survival (RFS), cystectomy-free survival (CFS),

KEY MESSAGES

- Sequential intravesical gemcitabine and docetaxel (gem/doce) may be considered a salvage therapy to limit progression for patients with BCG failure non-muscle-invasive bladder cancer.
- Gem/doce can allow some patients to safely delay radical surgery or even achieve a disease-free status.
- Gem/doce appears to be a safe and well-tolerated intravesical option.

cancer-specific survival (CSS), overall survival (OS), and treatment adverse events. Survival probabilities were estimated using the Kaplan-Meier method from the first gem/doce instillation.
Results: Thirty-five patients with a median age of 78 years old were included in the study. The median followup time was 21 months (interquartile range 10–29). More than 25% of patients received two or more prior BCG induction treatments. Overall/MIBC PFS estimates at one year were 85%/88% and 60%/70% at two years. Adverse events occurred in 37% of the patients, but only two patients didn't complete the treatment due to intolerance. Three patients underwent radical cystectomy due to cancer progression. OS was 94% at two years.
Conclusions: With 60% of PFS at two years, gem/doce appears to be a safe and well-tolerated option for BCG failure patients. Further studies are needed to justify widespread use.

INTRODUCTION

With nearly 12,000 Canadians diagnosed each year, bladder cancer is the 5th most common cancer in Canada.[1] More than 70% of new bladder cancer cases are non-muscle invasive bladder cancers (NMIBC).[2] Despite having a good prognosis, the high recurrence and the possibility of progression to muscle-invasive bladder cancer (MIBC), particularly for high-risk tumors, necessitate close surveillance and contribute to make NMIBC one of the most expensive per patient cancers to treat.[1,3]

For high-risk NMIBC, intravesical Bacillus Calmette-Guérin (BCG) is the standard adjuvant treatment to reduce recurrence and progression following complete transurethral resection of bladder tumor (TURBT).[4] However, despite adequate BCG administration, many patients with NMIBC either do not respond to treatment or have recurrence shortly after therapy. Tolerance of BCG treatments can also be a problem. Indeed, 40% to 50% of high-risk patients will experience BCG failure within 2 to 5 years while up to 5% will develop serious side effects leading to incomplete induction or maintenance BCG course.[5-8] In vulnerable populations such as older adults and immunocompromised individuals, there may also be diminished immunologic response to BCG which limits effectiveness.[9,10] Moreover, up to 10% of high-risk NIMBC will progress to muscle invasive bladder cancer (MIBC) following BCG treatment.[11,12] Recent data from our institution showed a progression of 8.1% at 3 years in high and very-high-risk patients, without any difference between sexes present.[13]

Guidelines suggest early radical cystectomy (RC) with pelvic lymphadenectomy as the standard treatment for patients who developed what is currently classified as BCG unresponsive NMIBC.[4] Retrospective studies suggest, survival rates among patients undergoing RC within two years of initial BCG are significantly higher than patients having surgery later.[14] Nevertheless, the surgical morbidity following RC can be significant with more than 60% of the patients experiencing complications and a 30-day mortality rate of 1.5%.[15] Further, many other

patients are not surgical candidates due to high perioperative risk or wish to preserve their bladder and quality of life.[16,17] Thus, there is a need to develop safer and more effective intravesical agents as alternative bladder preserving therapy.[4,18]

Sequential intravesical gemcitabine and docetaxel (Gem/Doce) is an emerging option for salvage therapy after BCG failure in patients with NMIBC. A recent multicentric study has reported a promising recurrence free survival (RFS) rate of 60% at 1 year and 46% at 2-year in a heterogenous cohort of BCG failure patients. Authors reported that sequential Gem/Doce was well-tolerated and considered effective in BCG failure patients.[19] In this study, we review our institution's experience of intravesical sequential Gem/Doce in BCG failure patients with NIMBC who were not candidates or declined radical cystectomy.

METHODS

Study design and population

This retrospective cohort study was approved by the Centre Hospitalier Universitaire (CHU) de Québec-Université Laval as part of a quality-of-care assessment in partnership with the pharmacy department. Exemption from review by the Institutional Review Board was granted according to article 2.5 of the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2) and the article 1.5 of the framework of the Research with humans' participants of the ministerial and social service of the government of Quebec. A waiver of informed consent was granted due to the use of deidentified data.

Using outpatient clinic and hospital pharmacy records, we retrospectively reviewed all BCG-failure patients with NMIBC who were not eligible or refused cystectomy and had been treated with Gem/Doce from April 2019 through October 2022 in the CHU de Québec-Université Laval.

Patients were included if they had a pathologic diagnosis of NMIBC and received at least 5/6 weekly intravesical instillations of sequential Gem/Doce after complete TURBT. All patients had previously completed at least one induction course of BCG, with or without subsequent maintenance. Patients were excluded if they received a palliative regimen of Gem/Doce in the context of a MIBC (n=1) or did not have any follow-up data (n=2).

Hospital charts were reviewed to collect demographic data, medical and bladder cancer treatment history, including BCG treatment dates and pathologic details of all tumor recurrences. Baseline tumor-risk stratification was done according to the 2021 European Association of Urology (EAU) NMIBC guideline and risk categories.[2]

BCG failure was defined according to CUA guidelines.[4] Briefly, BCG unresponsive was defined as recurrence pT1 high grade pathology at the first evaluation following adequate induction BCG, recurrent pTa high grade pathology within 6 months or recurrent CIS within 12 months after adequate induction (5/6) and at least 2/3 of a maintain or 2/6 second induction BCG. BCG relapsing referred to patient who achieve a complete response (CR) to BCG

treatment at six months but then experience any recurrence and BCG intolerant patients who experienced recurrences after an inadequate course of BCG due to severe adverse effects.[4]

Gemcitabine/docetaxel intravesical treatment

The Gem/Doce treatment protocol was administered as described by Steinberg et al. Briefly, patients received 1500 mg oral sodium bicarbonate the evening prior and the morning of treatment to alkalinize their urine. Intravesical instillation of 1gram gemcitabine in 50 ml normal saline for about 90 minutes was given followed by 37.5 mg docetaxel dissolved in 50 ml normal saline for 120 minutes.[19] This induction protocol was administered once a week for 6 weeks. Patient who responded to the induction treatment had maintenance instillations monthly with the same dosage and procedure for up to 2 years according to the physician's discretion.

Surveillance protocol

The first cystoscopy surveillance was initiated 6-8 weeks following initial induction completion. If disease free, interval follow-up cystoscopy and cytology were continued every 3 months for 2 years and every 6 months beyond 2 years following guidelines.[4] Bladder biopsies or TURBT was offered to patients with a positive cytology.

Analysis

Continuous variables (e.g., age, duration) were summarized using means, standard deviation, medians, minimum, maximums, and interquartile range as appropriate. Frequency and percentages were used to summarize categorical variables. The primary outcome was progression free survival (PFS) representing either NMIBC or MIBC progression.[20] NMIBC PFS was defined as a grade progression from LG to HG or a stage progression from Ta/CIS to T1 whereas MIBC PFS was defined as progression to ≥T2, lymph node or metastatic disease. Secondary outcomes included recurrence-free survival (RFS), defined as any pathologically confirmed tumor within the bladder, cystectomy-free survival (CFS), cancer-specific survival (CSS), overall survival (OS), adverse events and treatment tolerance judge by the attending urologist. Follow up was extended beyond first recurrence and if multiple progression occurred, only the first one was counted in the primary outcome. Survival analyses were based on the date of the first Gem/Doce instillation. Patients without recurrence or progression were censored at last follow-up cystoscopy. Survival probabilities were estimated using the Kaplan-Meier method and Log rank test were used to compare groups. All statistical analyses were performed using SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA) and Prism8 software (GraphPad Software, La Jolla, CA, USA).

RESULTS

Population

Between April 2019 through October 2022, 38 patients were treated with Gem/Doce. Three patients were excluded; Two were lost before initial follow-up and one received treatment in a MIBC palliative context, leaving 35 patients eligible for analyses (Figure 1). Table 1 shows the baseline demographic, clinical, pharmacological, and pathological characteristics of included patients. Among those patients, 27 (77%) were men and the median age at first instillation was 78 (IQR 69.0 - 83.0). Only 6% were active smokers at time of treatment. All patients received at least 1 complete induction of 5 or 6 BCG instillations and 26% had received 2 or more. The mean number of BCG instillations per patient was 12.4. Most patient (60%) were classified as BCG relapsing patients and 31% were BCG unresponsive. At the time of the TURBT prior to Gem/Doce, 77% patients had high-risk and 11% very high-risk features. Overall, CIS was present in 40% of patients; either isolated (20%) or in combination with HG pTa (9%) or HG pT1 (11%) disease (Table 1).

Oncologic outcomes

Table 2 shows the evolution of patients treated with sequential Gem/Doce. The median survival follow-up time was 21 months (IQR 10-29) and median follow-up time for progression and recurrence was 12.5 months (IQR 5.5-16.5). During follow-up, 16 (46%) patients had a recurrence. The RFS rate was 82%, 71% and 37% at 6 months, 1 year and 2 years, respectively. Recurrences were mostly HG (Figure 2). Eight (23%) patients had a progression (2 NMIBC progression and 6 MIBC progression). Overall PFS was 94% at 6 months, 85% at 1 year, and 60% at 2 years and MIBC PFS was 97% at 6 months, 88% at 1 year and 70% at 2 years. Three out of six patients with MIBC progression underwent RC at a median time of 11 months (range 6–16) after the first Gem/Doce instillation (Figure 3). In these patients, surgical pathology showed pT2N2, pT1N0 and pT3N3 disease. Of the other three patients who developed MIBC, one died of concomitant leukemia, one received palliative radiotherapy and the other declined any treatment and opted for palliative care. No patients died of bladder cancer and the overall survival was 94% (Figure 4).

Comparing separately patients who had HG pT1 disease (46%) or any CIS (40%), we found a 2-year PFS of 67% in the CIS group and 56% in the HG pT1, with no statistically significant difference between them. MIBC PFS was higher in the CIS group, with 91% at 2-year compared to 56% in the HG pT1. However, no statistically significant difference could be identified. Similarly, no difference was identified for the HG RFS between those 2 groups (Figure 5a-b). Finally, no RFS or PFS differences were identified between BCG relapsing/intolerant and BCG-unresponsive patients (Figure 6a-b).

Treatment safety

Thirteen (37%) patients experienced at least one adverse event throughout the course of treatment as summarized in Table 3. The most common reported adverse effects were urinary frequency/urinary urgency (24%) and dysuria (18%). One patient experienced either urinary retention, hematuria, fatigue, or nausea. Finally, while the treatment was temporarily suspended for 3 (9%) patients, only 2 (6%) patients did not complete the maintenance treatments due to intolerance.

DISCUSSION

Patients with recurrent high-risk NMIBC who do not respond to BCG remains a difficult population to treat. It is increasingly recognized that there is a window of opportunity to administer at least one course of second-line therapy after BCG before proceeding to RC, especially for patients with CIS or Ta tumors.[4] However, current guidelines do not recommend to prioritize a specific intravesical therapy for these patients since large prospective series are not mature and because the concerns persist of missing the window for cure. Indeed, Herr and Sogani identified an increased survival rate of 92% when RC was performed less than 2 years after initial BCG therapy vs 56% when the surgery was performed after 2 years from BCG.[14] In line with this, current guidelines recommend offering early RC whenever feasible for HG recurrent BCG unresponsive NMIBC following adequate BCG therapy.[4] Nevertheless, it is not always possible to safely perform a RC, as patients can be poor surgical candidates. Since perioperative complications such as morbidity, mortality, and long-term lifestyles changes are major concerns with RC, patients can also choose to delay surgery.[21, 22] In addition, some HG tumors like pTa tumors may have a lower propensity to progress to MIBC, making further intravesical therapy an interesting option to avoid overtreatment.[23]

Multiple studies have established sequential Gem/Doce as effective and safe to reduce the risk of recurrence of NMIBC in first and second-line setting.[24-30] While intravesical Gem/Doce has been shown to delay the time to recurrence, there is a paucity of data on whether it can impact time to local and systemic progression. Indeed, to safely delay cystectomy, it is crucial to ensure recurrences do not evolve in grade, stage, or metastatic disease. In this study, we describe a respectable PFS rate suggesting that intravesical sequential Gem/Doce is both a tolerable and efficacious intravesical option, in line with other recent reports.[24-30]

Other studies investigating this combination revealed similar results as our institutional experience with Gem/Doce. Steinberg et al. described in their multi-institutional study, a RFS of 60% at 1 year and 46% at 2 years with a heterogenous population of intermediate to high-risk NMIBC BCG failure patients.[19] NIMBC progression rate was not reported but 3.6% of the patient developed MIBC. A recent series described 96 patients treated with Gem/Doc for which 1- and 2-year MIBC PFS rates were higher (96% and 91%, respectively) than in our study. RFS in this series was also higher than ours.[31] These differences may be related to the higher percentage of patients with CIS (71%) or patient selection, with a higher proportion of patients in

their study undergoing early RC (21%). Nevertheless, both studies showed a relatively small percentage of progression at 2 years. Adverse events (37%) were slightly lower in our series than previously reported (nearly 50%), potentially due to shorter follow-up in our cohort.[31]

While subgroup sizes were limited, we could not detect clear differences regarding whether Gem/Doce may be more effective in CIS versus papillary tumors as suggested by others.[31,32] The lack of differences between patients with BCG failure or BCG unresponsive disease concurs with Chevuru et al.[31]

It is worthy to say that efficiency of Gem/Doce appears superior in BCG-naïve patients where one study demonstrated a 2-year RFS of 82%.[28] More recently, a ten-year cohort study has shown HG RFS of 81% at 24 months in Gem/Doce group against 69% at 24 months with BCG in first line treatment setting.[33]

When compared to other regimens, combination Gem /Doce seems to offer higher CR and clinical advantages.

Single-agent intravesical gemcitabine has shown less efficacy than Gem/Doce combination with 47.5% of RFS and 33% of progression at 15 months.[34] Another group reported that less than 30% of patients had a durable response with RFS rates of 28% and 21% at 1 and 2 years.[35] Other combination chemotherapies in NMIBC has proven superior efficacy than single agent, particularly in the BCG-failure category.[36] However, chemotherapy such as mitomycin C in association with BCG instillation was not superior to BCG monotherapy in the treatment of CIS.[37] Also, combination of gemcitabine and mitomycin C was tested and has demonstrated a RFS rates of 38% at 2 years post treatment.[38] The combination of Gem/Doce obtained better and lasting results suggesting a synergistic effect with these two chemotherapies.

Systemic immunotherapy has shown unprecedented responses in patients with metastatic urothelial cancer, encouraging investigators to explore this kind of treatment in early urothelial cancer stages.[39-42] FDA approved pembrolizumab (PD-1-Inhibitor) in BCG unresponsive CIS after the KEYNOTE-057. This Phase II study has shown a CR in the CIS arm of 41% at first cystoscopy with a RFS of 19% at 1-year and 11% at 2-year. Grade 3-4 adverse events have been reported in 12 % of the patients. However, the use of pembrolizumab is limited outside the USA by his potential systemic toxicity, intravenous administration, and cost. Also, the single-arm trial design impedes cost reimbursement of the responsible payers. [43] Phase II trials SWOG 1605 assessed Atezolizumab (PD-L1 Inhibitor) in 73 BCG unresponsive CIS patients reporting a CR at 3 and 6 months of 41% and 26%, respectively.[44]

Viral and gene therapy such as intravesical nadofarogene firadenovec, has also been recently FDA approved. Phase III study reported overall 1 year CR of 30% and 1 year CR of 24% and 43% for CIS only and HG Ta or T1, respectively.[45] CG0070, a cancer selective replication competent adenovirus, has shown in Phase II trial with BCG unresponsive patients an overall 6, 12 and 18 months CR rates of 47%, 30% and 21% respectively.[46] Although many trials and options are still under clinical development, combination Gem/Doce has the advantage to be

already evaluable in hospitals with oncology pharmaceutical laboratory and to be cost effective, especially when compared to immunotherapy.[47]

Key strengths of our study include a cohort mostly compose of high and very-high risk NMINC who failed BCG treatment. Further, we provide details on both progression by both grade and stage. As our health-care system is universal and publicly funded, our institution is the sole provider of BCG and Gem/Doce treatments for the local population, decreasing potential biases due to socio-economic status or referral biases. However, our institution provides service for a very large territory, and it may be inconvenient or impossible for some patients who lives far from the treating hospital to travel on a weekly basis for an induction course. The detailed review of patient charts and pharmacy records provides important medical details pertinent to prior BCG receipt and Gem/Doce outcomes. Another strength in our study includes a standardized protocol based on previous studies which was applied by an experienced team.

The inherent limitations of retrospective single-institution series apply to our study. As it is a new treatment regimen in our institution, this study is also limited by the relatively moderate size of the cohort and the limited follow-up period. Indeed, no statistical differences in our subgroups could be tested given the cohort size. Furthermore, while we observed a greater proportion of MIBC progression, the size of the cohort did not allow us to highlight a population more at risk of developing MIBC. As our cohort was mainly composed of patient with HG pT1, we can speculate that it skews the results in favor of progression to MIBC. Finally, adverse events were compiled based on nursing notes but did not use a validated questionnaire, nor was a consistent grading system applied. Thus, it is possible we may have underestimated their prevalence. However, while prospective adverse event grading was not performed, only 2 patients had severe reactions that might have constituted a grade 3 or higher event, leading to discontinuation of treatment. Additionally, no adverse events appeared to last longer than 2 weeks after the last instillation.

CONCLUSIONS

In summary, we describe a cohort of patients BCG failure NMIBC who received sequential intravesical Gem/Doce. Even if there is no evidence-based management algorithm for salvage intravesical therapy in BCG failure NMIBC, this study provides additional data suggesting that Gem/Doce can allow some patients who are not eligible for research protocols or refused RC to safely delay surgery or achieve a disease-free status. Larger prospective series with BCG unresponsive patients stratified according to CIS or papillary tumors are needed to achieve better counselling and lead to guidelines changes.

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FIGURES AND TABLES

Figure 1. Inclusion/exclusion flowchart.

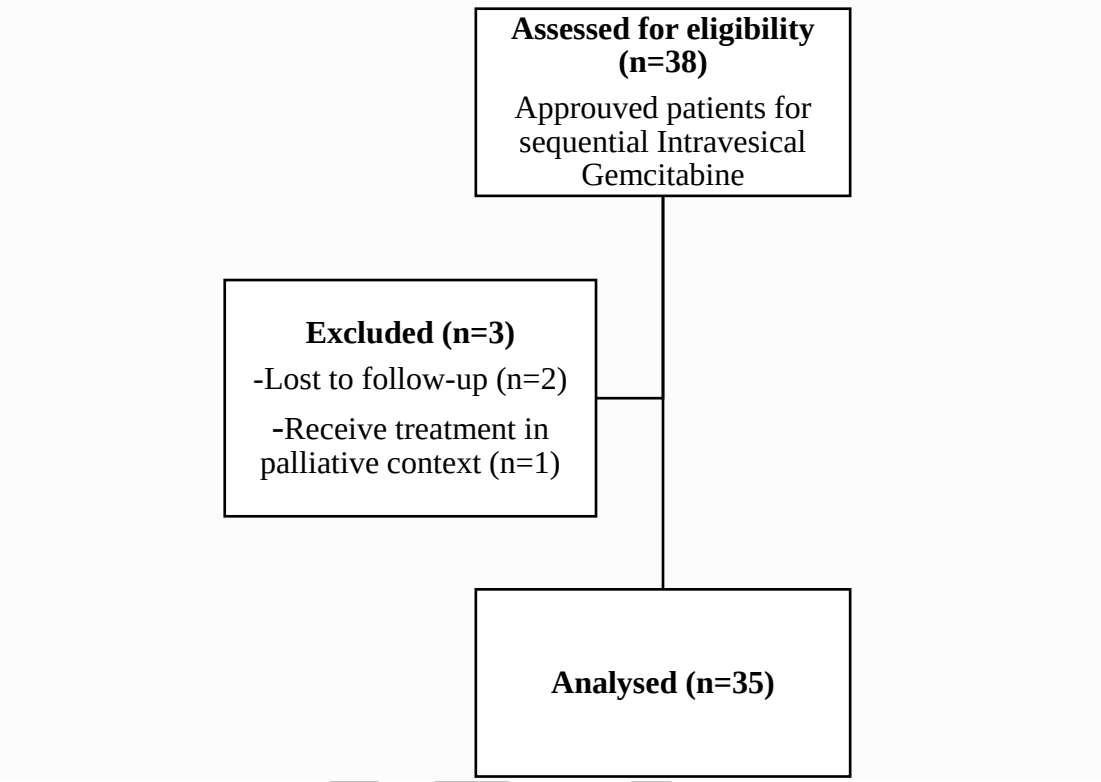

Figure 2. Overall recurrence-free survival (RFS) and high-grade RFS in 35 patients treated with gemcitabine/docetaxel.

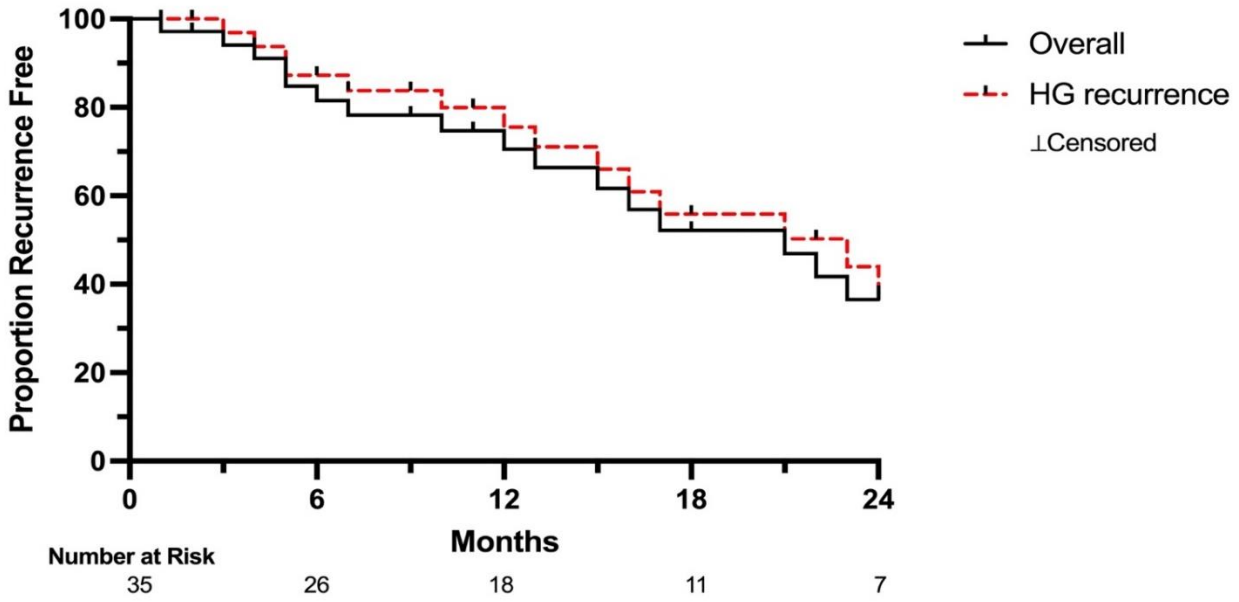

Figure 3. Overall progression-free survival (PFS), non-muscle-invasive bladder cancer (NMIBC) PFS, muscle-invasive bladder cancer (MIBC) PFS, and cystectomy-free survival in 35 patients treated with gemcitabine/docetaxel.

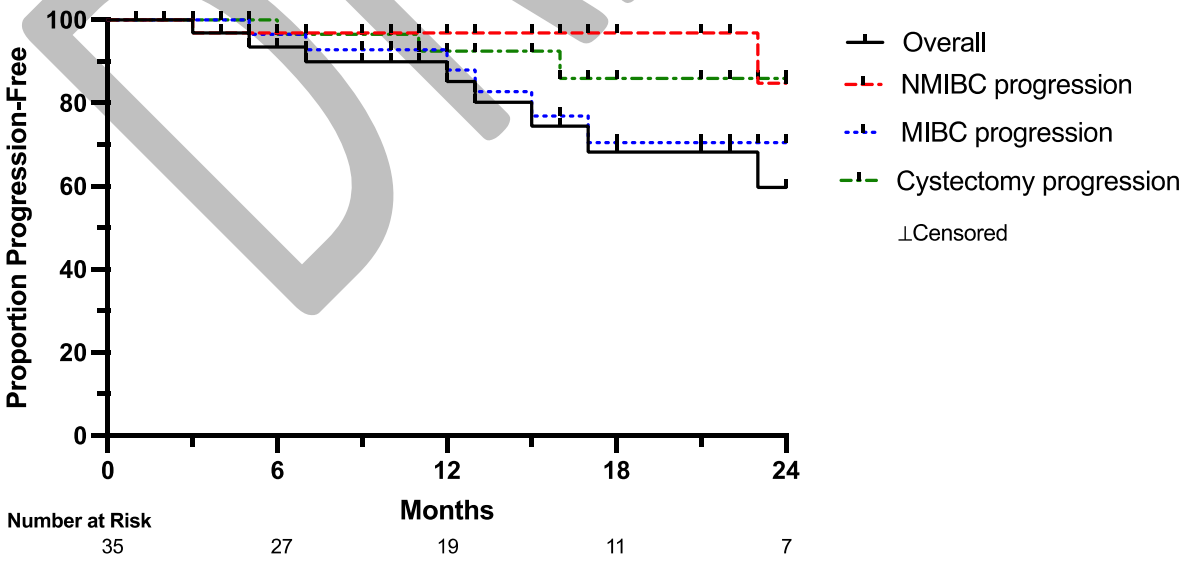

Figure 4. Overall survival and cancer-specific survival in 35 patients treated with gemcitabine/docetaxel.

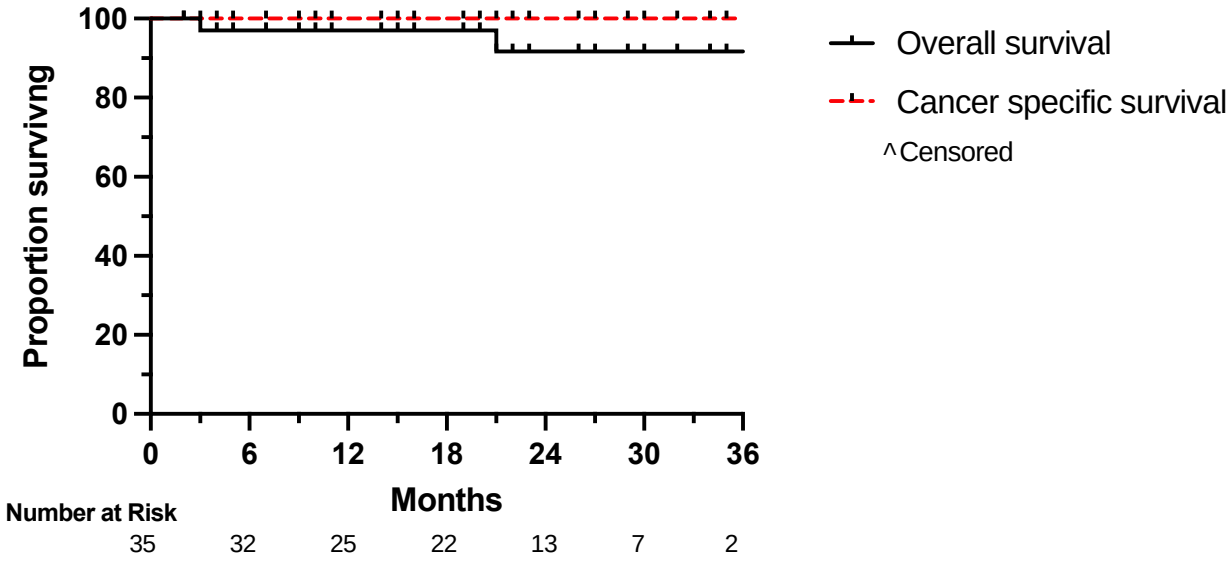

Figure 5. (A) High-grade tumor (HG) recurrence-free survival in T1HG vs. any carcinoma in situ (CIS). (B) Muscle-invasive bladder cancer progression-free survival in T1HG vs. any CIS.

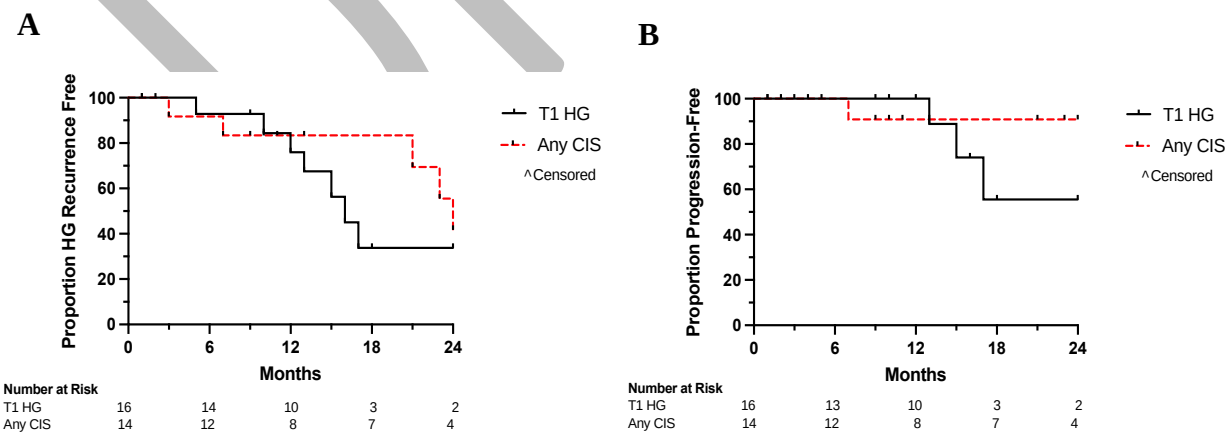

Figure 6. (A) High-grade tumor (HG) recurrence-free survival in bacillus Calmette-Guérin (BCG) failure vs. BCG unresponsive. (B) Muscle-invasive bladder cancer progression-free survival in BCG failure vs. BCG unresponsive

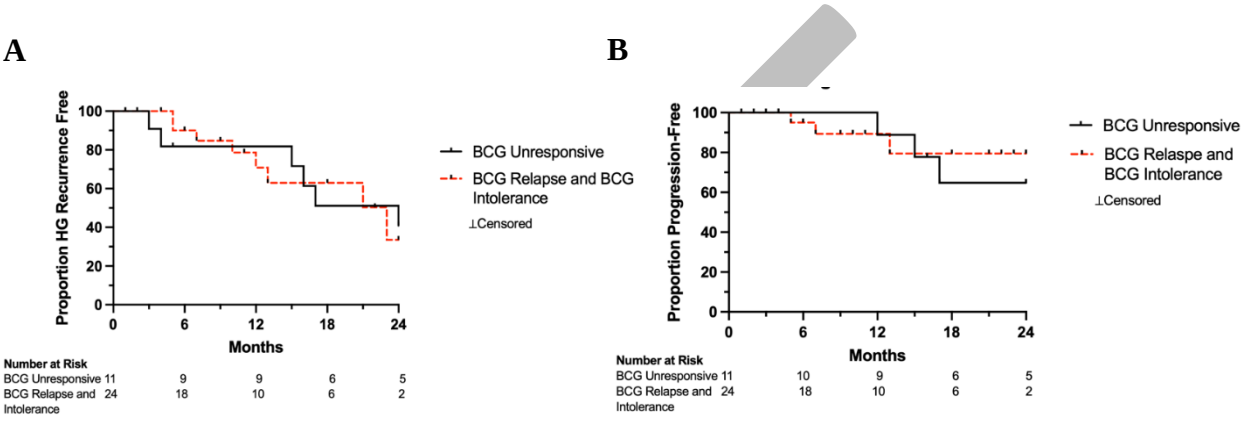

Table 1. Patient characteristic at treatment initiation with gemcitabine/docetaxel	
Parameters	**N=35 (%)**
Male	27 (77)
Age	78.0 [69.0–83.0]
Active smoker	2 (6)
Prior BCG induction:	
1 induction	35(100)
2 inductions	9 (26)
3 inductions	2 (6)
Total instillation	12.4±8.3
BCG failure	
BCG unresponsive	11 (31)
BCG relapse	21 (60)
BCG intolerance	3 (9)
Risk stratification	
Intermediate risk	4 (11)
High-risk	27 (77)
Very high-risk	4 (11)

Pre-gem/doce pathology	
CIS	7 (20)
LG pTa	4 (11)
HG pTa	5 (14)
HG pTa + CIS	3 (9)
HG pT1	12 (34)
HG pT1 + CIS	4 (11)
Any CIS	14 (40)

Results are means ± standard deviation, n (%), or median [25th–75th percentiles]. BCG: bacillus Calmette-Guérin; CIS: carcinoma in situ.

Table 2. Evolution in patients treated with sequential gemcitabine/docetaxel

Parameters	**Overall N=35 (%)**	**NMIBC**	**MIBC**	**HG**
Median followup for survival	21.0 months [10.0–29.0]			
Patient with progression during followup	8 (23)	2 (6)	6 (17)	
Progression-free survival				
6 months	94%	97%	97%	
12 months	85%	97%	88%	
24 months	60%	85%	70%	
Patient with recurrence during followup	16 (46)			
Recurrence-free survival				
6 months	82%			87%
12 months	71%			76%
24 months	37%			38%
Progression to cystectomy during followup	3 (9)			
Cystectomy-free survival				
6 months	97%			
12 months	93%			
24 months	88%			
Deceased during followup	2 (6)			
Died of bladder cancer	0			
Overall survival at 24 months	94%			

Results are median [25th–75th percentiles], percentage, and n (%). HG: high-grade tumor; MIBC: muscle-invasive bladder cancer; NMIBC: non-muscle-invasive bladder cancer.

Table 3. Adverse events reported in patients treated with sequential gemcitabine/docetaxel	
Parameters	**N=35 (%)**
Patient experiencing adverse events	13 (37)
Urinary urgency	8(24)
Dysuria	6 (18)
Hematuria	1 (3)
Urinary retention	1 (3)
Nausea	1 (3)
Fatigue	1 (3)
Patient treatment schedule affected by side effects	3 (9)
Treatment incomplete due to intolerance	2 (6)

Results are n (%).