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

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Cite as: Garneau C-A, Marcotte N, Lacombe L, et al. Salvage therapy for BCG failure with intravesical sequential gemcitabine and docetaxel in patients with recurrent NMIBC. *Can Urol Assoc J* 2024;18(2):33-40. http://dx.doi.org/10.5489/cuaj.8341

Published online October 23, 2023

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 NMIBC patients with BCG failure 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), 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 and MIBC PFS estimates at one year were 85%and 88%, and at two years, 60% and 70%, respectively. Adverse events occurred in 37% of the patients, but only two patients didn't complete the treatment due to intolerance. Three patients underwent RC 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 fifth 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 making 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, 40–50% of high-risk patients will experience BCG failure within 2–5 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 MIBC following BCG treatment.[11,12] Recent data from our institution showed a progression of 8.1% at three 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 their 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 one year and 46% at two years 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 for or declined RC.

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 NMIBC patients with BCG failure 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 followup data (n=2).

Hospital charts were reviewed to collect demographic data, as well as 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 of pT1 high-grade pathology at the first evaluation following adequate induction BCG, recurrent pTa high-grade pathology within six months or recurrent carcinoma in situ (CIS) within 12 months after adequate induction (5/6) and at least 2/3 of a maintenance 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 experienced 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 1 g 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 six weeks. Patients who responded to the induction treatment had maintenance instillations monthly with the same dosage and procedure for up to two years at the physician's discretion.

Surveillance protocol

The first cystoscopy surveillance was initiated 6–8 weeks following initial induction completion. If disease-free, interval followup cystoscopy and cytology were continued every three months for two years and every six months beyond two 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 (IQR) 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 low-grade to high-grade 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 judged by the attending urologist.

Followup was extended beyond first recurrence and if multiple progressions 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 followup cystoscopy. Survival probabilities were estimated using the Kaplan-Meier method and log rank test was used to compare groups. All statistical analyses were performed using SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, U.S.) and Prism8 software (GraphPad Software, La Jolla, CA, U.S.).

RESULTS

Population

Between April 2019 and October 2022, 38 patients were treated with gem/doce. Three patients were excluded; two were lost before initial followup and one received treatment in a MIBC palliative context, leaving 35 patients eligible for analyses. 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 the time of treatment. All patients received at least one complete induction of five or six BCG instillations and 26% had received two or more. The mean number of BCG instillations per patient was 12.4. Most patients (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 high-grade pTa (9%) or high-grade pT1 (11%) disease (Table 1).

Oncologic outcomes

Table 2 shows the evolution of patients treated with sequential gem/doce. The median survival followup time was 21 months (IQR 10–29) and median followup

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.

time for progression and recurrence was 12.5 months (IQR 5.5–16.5). During followup, 16 (46%) patients had a recurrence. The RFS rates were 82%, 71%, and 37% at six months, one year, and two years, respectively. Recurrences were mostly high-grade (Figure 1). Eight (23%) patients had a progression (two NMIBC progression and six MIBC progression). Overall PFS was 94% at six months, 85% at one year, and 60% at two years, and MIBC PFS was 97% at six months, 88% at one year, and 70% at two 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 2). 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 OS was 94% (Figure 3).

Comparing separately patients who had high-grade pT1 disease (46%) or any CIS (40%), we found a two-year PFS of 67% in the CIS group and 56% in the high-grade pT1, with no statistically significant difference between them. MIBC PFS was higher in the CIS group, with 91% at two years compared to 56% in the high-grade pT1 group; however, no statistically significant difference could be identified. Similarly, no difference was identified for the high-grade RFS between those two groups (Figures 4A, 4B). Finally, no RFS or PFS differences were identified between BCG-relapsing/intolerant and BCG-unresponsive patients (Figures 5A, 5B).

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 each experienced either urinary retention, hematuria, fatigue, or nausea. Finally, while the treatment was temporarily suspended for three (9%) patients, only two (6%) patients did not complete the maintenance treatments due to intolerance.

DISCUSSION

Patients with recurrent high-risk NMIBC who do not respond to BCG remain 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 prioritizing 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 two years after initial BCG therapy vs. 56% when the surgery was performed after two years from BCG.[14]

In line with this, current guidelines recommend offering early RC whenever feasible for high-grade, 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 high-grade 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 the first- and second-line settings.[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 to our institutional experience with gem/doce. In their multi-institutional study, Steinberg et al described a RFS of 60% at one year and 46% at two 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/doce for which one- and two-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 two years. Adverse events (37%) were slightly lower in our series than previously reported (nearly 50%), potentially due to shorter followup 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 vs. 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 worthwhile to note that efficiency of gem/doce appears superior in BCG-naive patients, where one study demonstrated a two-year RFS of 82%.[28] More recently, a 10-year cohort study has shown high-grade RFS of 81% at 24 months in the gem/doce group against 69% at 24 months with BCG in the 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% RFS and 33% progression at 15 months.[34] Another group reported that <30% of patients had a durable response, with RFS rates of 28% and 21% at one and two years, respectively.[35] Other combination chemotherapies in NMIBC have shown superior efficacy than single agents, particularly in the BCG-failure category;[36] however, chemotherapy, such as mitomycin C, in association with

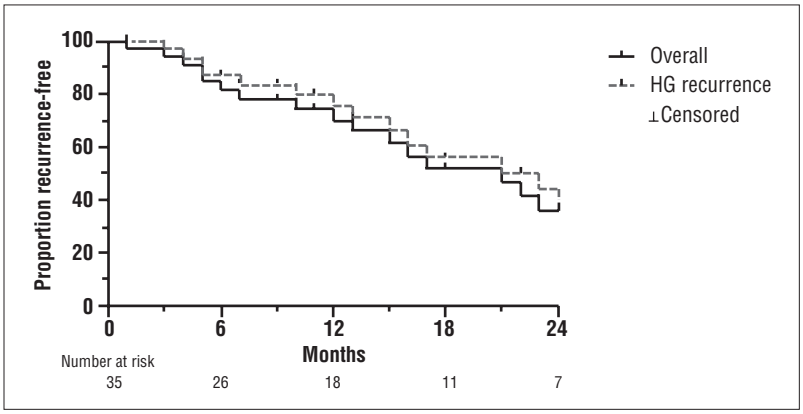

Figure 1. Overall recurrence-free survival (RFS) and high-grade (HG) RFS in 35 patients treated with gemcitabine/docetaxel.

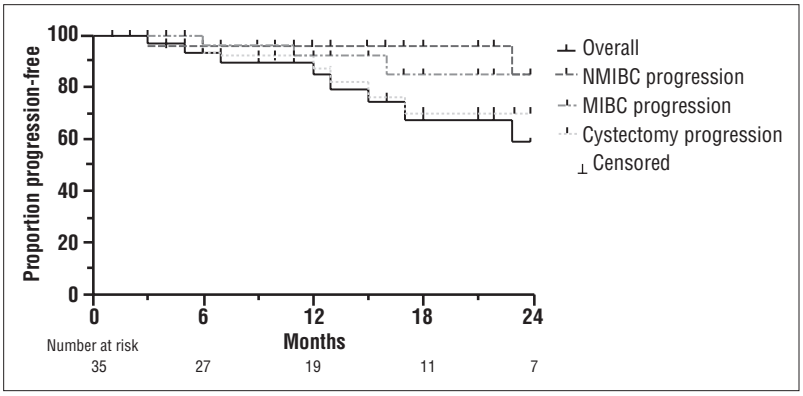

Figure 2. Overall progression-free survival (PFS), non-muscle-invasive bladder cancer (NMIBC) PFS, muscle-invasive bladder cancer (MIBC) PFS, and cystectomy-free survival in 35 patients treated with gemcitabine/docetaxel.

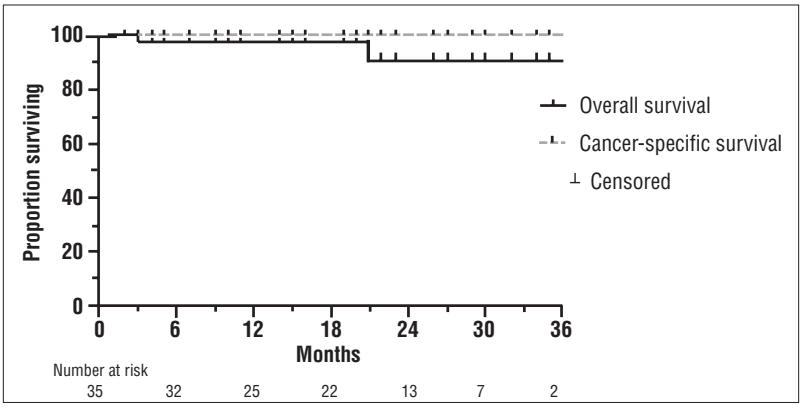

Figure 3. Overall survival and cancer-specific survival in 35 patients treated with gemcitabine/docetaxel.

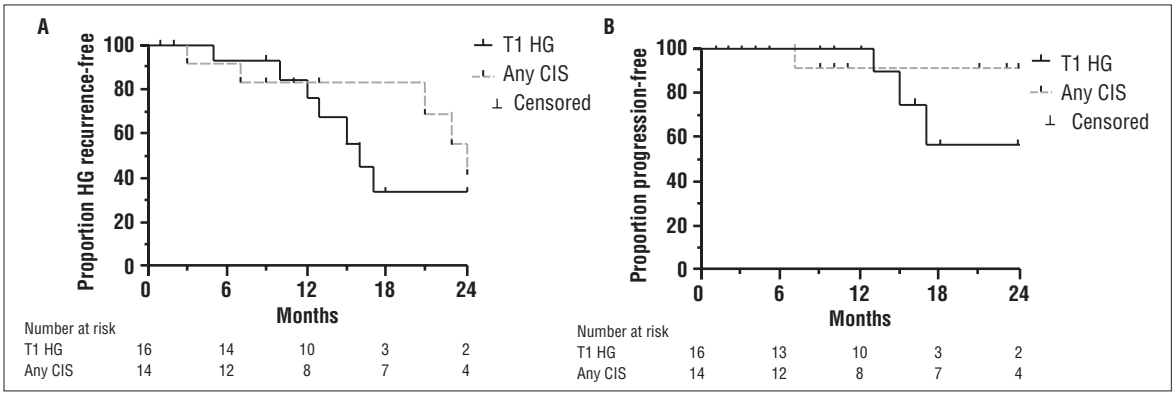

Figure 4. (A) High-grade tumor (HG) recurrence-free survival in T1HG vs. any carcinoma in situ (CIS). (B) Muscle-invasive bladder cancer progression-free survival in T1HG vs. any CIS.

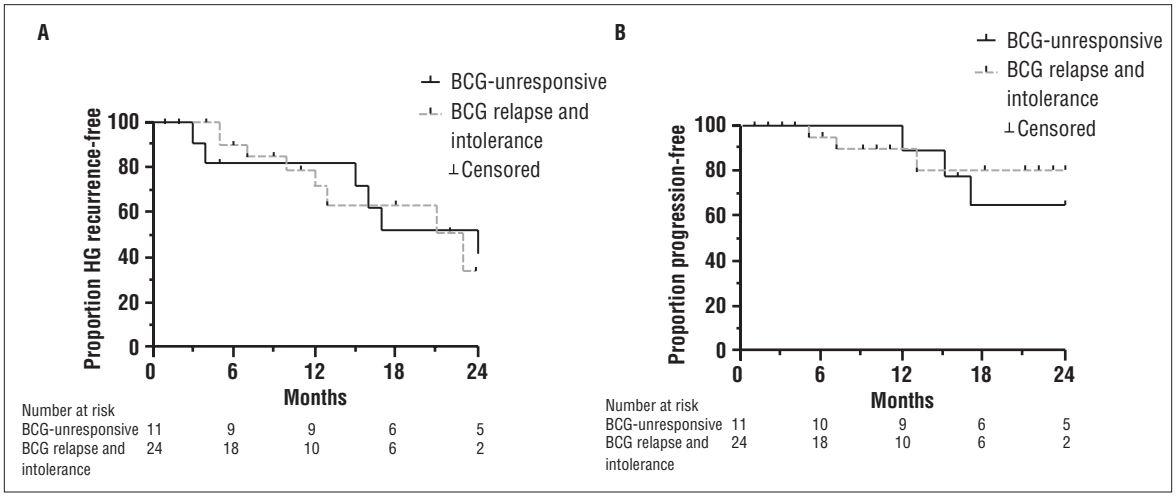

Figure 5. (A) High-grade tumor (HG) recurrence-free survival in bacillus Calmette-Guérin (BCG) failure vs. BCG unresponsive. (B) Muscle-invasive bladder cancer progression-free survival in BCG failure vs. BCG unresponsive

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 rate of 38% at two years post-treatment.[38] The combination of gem/doce obtained better and more 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] The FDA approved pembrolizumab (PD-1-Inhibitor) in BCG-unresponsive CIS after release of the KEYNOTE-057 results. This phase 2 study showed a CR in the CIS arm of 41% at first cystoscopy, with a RFS of 19% at one year and 11% at two years. Grade 3–4 adverse events have been reported in 12 % of patients; however, the use of pembrolizumab is limited outside the U.S. by its potential systemic toxicity, intravenous administration, and cost. Also, the single-arm trial design impedes cost reimbursement of the responsible payers.[43] The phase 2 trial, SWOG 1605, assessed atezolizumab (PD-L1 Inhibitor) in 73 BCG-unresponsive CIS patients, reporting a CR at three and six months of 41% and 26%, respectively.[44]

Viral and gene therapies, such as intravesical nadofarogene firadenovec, have also been recently FDA-approved. A phase 3 study reported an overall one-year CR of 30% and a one-year CR of 24% and 43% for CIS only and high-grade Ta or T1, respectively.[45] In phase 2 trials with BCG-unresponsive patients, CG0070, a cancer selective replication competent adenovirus, has shown overall six-, 12-, and 18-month 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 of already being available in hospitals and with oncology pharmaceutical laboratories, as well as being cost-effective, especially when compared to immunotherapy.[47]

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 (%).

Strengths and limitations

Key strengths of our study include a cohort mostly composed of high- and very high-risk NMINC patients who failed BCG treatment. Further, we provide details on progression by both grade and stage. As our healthcare 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 socioeconomic status or referral biases; however, our institution provides service for a very large territory, and it may be inconvenient or impossible for patients who live 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 is that our study includes a standardized protocol based on previous studies, applied by an experienced team.

The inherent limitations of a retrospective, single-institution series apply to our study. As the treatment evaluated is a new regimen in our institution, this study is also limited by the relatively moderate size of the cohort and the limited followup 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 patients with high-grade 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 two 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 two weeks after the last instillation.

CONCLUSIONS

We describe a cohort of NMIBC patients with BCG failure 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 ineligible 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 guideline changes.

COMPETING INTERESTS: Dr. Pouliot has been an advisory board member for Amgen, Astellas, Astra Zeneca, Bayer, Janssen, Novartis, TerSera, and Tolmar; and has received grants/honoraria from Astellas and Merck. Dr. Toren has been an advisory board member for Abbvie, Bayer, and Knight; has received grants/honoraria from AstraZeneca; and has participated in clinical trials supported by Janssen Merck, and Roche. All other authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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