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Sequential Intravesical Gemcitabine and Docetaxel for bacillus Calmette-Guérin-Naïve High-Risk Nonmuscle-Invasive Bladder Cancer

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Study Need and Importance: High-risk nonmuscle-invasive bladder cancer (NMIBC) poses significant risk of recurrence and progression. Bacillus Calmette-Guérin (BCG) is currently recommended as the gold standard adjuvant therapy following complete transurethral resection of bladder tumor. Continued production issues have precluded use of BCG in many urological practices. Furthermore, the efficacy and tolerance of BCG is suboptimal. Given these factors, there has been increasing interest and utilization of alternative first-line intravesical therapies. Given ongoing BCG shortages, our institution has transitioned to use of sequential intravesical gemcitabine and docetaxel (Gem/Doce) in the first-line setting.

What We Found: We analyzed a cohort of 107 patients with high-risk BCG-naïve NMIBC treated with Gem/Doce. Patients had high-risk characteristics including 47 with any carcinoma *in situ* and 55 with T1 disease. Median followup was 15 months. Recurrence-free survival was 89%, 85% and 82% at 6, 12 and 24 months, respectively (see Figure). The recurrence rates were not affected when the cohort was stratified by presence of carcinoma *in situ*. No patients developed disease progression or died of bladder cancer. One patient underwent cystectomy for end-stage lower urinary tract symptoms. Overall survival was 84% at 2 years. The treatment was well tolerated, with only 4 patients unable to tolerate a full induction course of Gem/Doce. The most commonly reported side effect was frequency/urgency occurring during instillation.

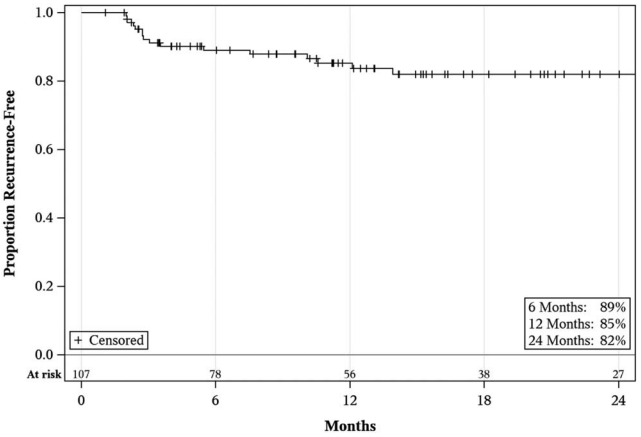

Figure. Recurrence-free survival following Gem/Doce induction.

Limitations: This study is limited by its retrospective nature and lack of a comparator arm, allowing for potential selection bias. Furthermore, these results are from a high-volume institution with rigorous NMIBC protocols that may limit generalizability.

Interpretation for Patient Care: Our results demonstrate that Gem/Doce is a safe and effective adjuvant treatment for patients with high-risk NMIBC. Compared to BCG, this treatment is readily available, cheap and not subject to supply constraints. While prospective validation is needed, in the setting of chronic BCG shortage, Gem/Doce represents a valuable alternative treatment option for patients with NMIBC.

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Sequential Intravesical Gemcitabine and Docetaxel for bacillus Calmette-Guérin-Naïve High-Risk Nonmuscle-Invasive Bladder Cancer

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Abbreviations and Acronyms

BCG = bacillus-Calmette Guérin
CIS = carcinoma *in situ*
CTCAE = Common Terminology Criteria for Adverse Events
DOR = duration of response
Gem/Doce = gemcitabine and docetaxel
HG = high-grade
LG = low-grade
NMIBC = nonmuscle-invasive bladder cancer
OS = overall survival
RFS = recurrence-free survival
TURBT = transurethral resection of bladder tumor

Purpose: Bacillus Calmette-Guérin (BCG) is currently recommended as adjuvant therapy following complete transurethral resection of bladder tumor for high-risk nonmuscle-invasive bladder cancer (NMIBC). In response to the BCG shortage, gemcitabine plus docetaxel (Gem/Doce) has been utilized at our institution in the BCG-naïve setting. We report the outcomes of patients with high-risk BCG-naïve NMIBC treated with Gem/Doce.

Materials and Methods: We retrospectively reviewed patients with BCG-naïve high-risk NMIBC treated with Gem/Doce from May 2013 through April 2021. Patients received 6 weekly intravesical instillations of sequential 1 gm gemcitabine and 37.5 mg docetaxel after complete transurethral resection of bladder tumor. Monthly maintenance of 2 years was initiated if disease-free at first followup. The primary outcome was recurrence-free survival. Survival was assessed with the Kaplan-Meier method, indexed from the first Gem/Doce instillation. Adverse events were reported using CTCAE (Common Terminology Criteria for Adverse Events) v5 (National Cancer Institute, Bethesda, Maryland). Differences were assessed with the log-rank test.

Results: There were 107 patients with a median followup of 15 months included in the analysis. Patients had high-risk characteristics including 47 with any carcinoma *in situ* and 55 with T1 disease. Recurrence-free survival was 89%, 85% and 82% at 6, 12 and 24 months, respectively. Recurrence rates were similar between patients with or without carcinoma *in situ* ($p=0.42$). No patient had disease progression or died of bladder cancer. One patient underwent cystectomy due to end-stage lower urinary tract symptoms. Overall survival was 84% at 24 months. There were 92 adverse events (1 ≥grade 3), and 4 (4%) patients were unable to receive a full induction course.

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Ethics Statement: Study received Institutional Review Board approval (IRB No. 201404766).
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Editor's Note: This article is the first of 5 published in this issue for which Category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 746 and 747.

See Editorial on page 526.

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Conclusions: Gem/Doce is an effective and well-tolerated therapy for BCG-naïve NMIBC. Further investigation is warranted.

Key Words: instillation; drug; urinary bladder neoplasms; docetaxel; gemcitabine; urinary bladder

An estimated 83,000 new cases of bladder cancer will occur in the United States in 2021 with over 75% being nonmuscle-invasive bladder cancer (NMIBC).[1,2] High-risk NMIBC poses increased risk of progression and requires aggressive treatment. Thus, various guidelines recommend administration of bacillus Calmette-Guérin (BCG) as adjuvant therapy following complete transurethral resection of bladder tumor (TURBT).[2,3] Unfortunately, BCG production shortages continue to be a chronic problem and preclude the use of BCG in many urological practices.[4] Beyond availability, BCG efficacy remains suboptimal (up to 40% failure rate at 2 years[5]) and tolerance is problematic.[6] Given these factors, there has been increasing interest and utilization of alternative intravesical therapies in both the first-line and salvage treatment settings.

Prior prospective studies have consistently demonstrated the superiority of BCG to single-agent chemotherapy regimens in the BCG-naïve setting.[7,8] However, combination chemotherapy regimens have not been as rigorously assessed for these patients. Sequential intravesical gemcitabine and docetaxel (Gem/Doce) was first reported in 2014 as an efficacious and well tolerated therapy for patients in whom BCG had failed.[9] Since this time, these results have been corroborated in large multi-institutional cohorts.[9,10] In light of these data and in response to the continuing BCG shortage, several institutions have adopted utilization of Gem/Doce in the BCG-naïve setting, although robust data supporting this practice are lacking thus far.[11,12] Our practice has gradually transitioned to almost exclusive use of Gem/Doce as the first-line treatment of high-risk NMIBC. Herein, we report outcomes of a large cohort of patients with high-risk BCG-naïve NMIBC treated with Gem/Doce as a first-line therapy.

MATERIALS AND METHODS

Study Design and Population

After obtaining Institutional Review Board approval (IRB No. 201404766), we retrospectively reviewed all patients with BCG-naïve high-risk NMIBC who were treated with sequential intravesical Gem/Doce between May 2013 and April 2021. Patients were included if intended to receive 6 weekly intravesical instillations of sequential 1 gm gemcitabine and 37.5 mg docetaxel after complete TURBT, even if fewer instillations were administered. There were 89 patients who received complete TURBT at our institution prior to Gem/Doce induction. Seventy-seven of these included adjunctive blue light cystoscopy. At 3-month surveillance, 88 of 107 patients received adjunctive blue light cystoscopy. In most cases of T1 disease, our institutional protocol is to perform repeat TURBT. However, there were 22 included patients with T1 disease who did not receive repeat transurethral resection prior to Gem/Doce. In these cases, repeat TURBT was postponed until 3 month surveillance or replaced with formal restaging due to favorable risk factors such as unifocal disease, small tumor size and minimal T1 involvement. Patients were excluded if they received a preoperative or palliative regimen of Gem/Doce in the setting of known muscle-invasive or metastatic disease. High-risk status was as defined by American Urological Association criteria.[2] Patients were excluded if they did not undergo at least 1 followup surveillance visit.

Gem/Doce Therapy

The Gem/Doce treatment protocol was performed as has been previously reported.[9] In brief, patients were sequentially treated with 1 gm gemcitabine in 50 ml sterile water (or normal saline) for 90 minutes followed by 37.5 mg docetaxel dissolved in 50 ml normal saline for 90−120 minutes. Patients were instructed to refrain from urinating for 60−120 minutes following Gem/Doce instillation. If tumor burden was reported on the dome or lateral wall surfaces, the patient was instructed roll and switch positions during the instillation to maximize affected bladder wall contact. Induction treatments were scheduled once a week for 6 weeks. Patients were treated with 1,300 mg oral sodium bicarbonate the evening prior and the morning of treatment to alkalinize the urine. Oral ondansetron and naproxen were administered as needed for nausea or bladder pain, respectively. Whenever possible, if disease-free at first followup, monthly maintenance therapy was given for up to 24 months. Maintenance instillation procedures and dosages matched those used in the induction protocol.

Surveillance

Surveillance took place 12 to 16 weeks after initial Gem/Doce instillation and involved either formal restaging under anesthesia or office cystoscopy. Restaging procedures included cystoscopy (with blue light if available), bladder barbotage cytology, bilateral upper tract barbotage cytologies, bilateral retrograde pyelograms, random bladder biopsies and prostatic urethral biopsies. Upper tract imaging was obtained every 1−2 years. Patients with negative cystoscopy and positive cytology or fluorescence *in situ* hybridization underwent restaging TURBT. Patients with low-grade (LG) or benign recurrences received repeat TURBT or office fulguration and were considered for extended maintenance therapy. If disease-free, repeat surveillance cystoscopy with bladder

cytology was performed every 3 months for 2 years, and every 6 months afterward.

Analysis

Data were retrospectively collected and stored in a REDCap™ database supported by the University of Iowa National Institutes of Health/Clinical and Translational Science Awards Program Grant UL1TR002537. Patient clinicopathological features, treatment history and oncologic outcomes were analyzed. Data were also collected regarding tolerance of treatment and modifications to instillation regimens. The primary outcome was recurrence-free survival (RFS) and efficacy was evaluated in an intention-to-treat manner. Recurrence was defined as tumor relapse in the bladder or prostatic urethra in males. Secondary outcomes included high-grade RFS, progression-free survival, cancer-specific survival, duration of response (DOR) and overall survival (OS). Survival probabilities were plotted using the Kaplan-Meier method, and group comparisons were made using the log-rank test. Estimates along with 95% pointwise confidence intervals were reported. Time was calculated from the start of Gem/Doce induction. Progression-free survival was defined by recently updated International Bladder Cancer Group guidelines; progression events included T stage increase from Ta or carcinoma *in situ* (CIS) to T1, development of T2 or greater disease, or lymph node or metastatic disease.[13] Adverse events were abstracted from patient charts based on reported symptoms and impact on treatment schedule, and classified by the Common Terminology Criteria for Adverse Events (CTCAE) v5 (National Cancer Institute, Bethesda, Maryland). Patients were defined as being intolerant to Gem/Doce if the treatment course was stopped due to symptoms or any serious adverse event. All statistical testing was 2-sided and assessed for significance at the 5% level using SAS® v9.4 (SAS Institute, Cary, North Carolina). A *post hoc* sensitivity analysis was performed to assess the impact of changes in Gem/Doce utilization over time. Analysis was stratified before and after 2019, when Gem/Doce was utilized almost exclusively as first-line therapy for high-risk NMIBC due to BCG shortage.

RESULTS

Demographics

The final cohort included 107 patients with high-risk NMIBC (Table 1). This group had high risk features including 44% with either isolated CIS (15%) or in combination with Ta/T1 disease (29%). Furthermore, 52% of patients had stage T1 high-grade (HG) disease. There were 7 (7%) patients with variant histology, all of whom had a component of micropapillary histology. Of these, 5 were negative for variant histology on re-resection and 1 was reported as micropapillary component comprising <1% of total tumor burden. A total of 85 (88%) eligible patients received monthly maintenance instillations. Reasons for not receiving maintenance therapy included toxicity, scheduling logistics and loss to followup.

Tolerance

Sixty (56%) patients reported at least 1 adverse event throughout the course of treatment, of whom 9 patients had symptoms that affected the treatment schedule (Table 2). There were 100 (94%) patients who received the full 6-week induction course and 97% who received at least 5/6 treatments. There were 4 patients (3.7%) who did not receive a complete induction course due to intolerance. Treatment was stopped in 3 patients due to hematuria and in 1 patient due to frequency/nocturia. There were a total of 92 adverse events, of which 31 were grade 1, 60 were grade 2 and 1 was grade 3. The grade 3 event was an emergency department visit for atrial fibrillation following a monthly maintenance instillation. No further problems were reported, and the patient continued with Gem/Doce therapy. The most commonly reported side effect was urinary frequency/urgency comprising 50% of all reported side effects and approximately two-thirds of all grade 2 events. Other commonly reported side effects included hematuria and dysuria, comprising 17% and 11% of all reported side effects, respectively.

Table 1. *Clinical pathological features in 107 BCG-naïve NMIBC patients treated with sequential Gem/Doce*

Median yrs age (IQR)	76	67–83
No. gender (%):		
Female	17	(16)
Male	90	(84)
No. race (%):*		
Non-White	4	(3.8)
White	102	(96)
No. smoking status (%):*		
Never-smoker	32	(30)
Former smoker	61	(58)
Current smoker	13	(12)
Pre-Gem/Doce pathology (%):		
CIS	16	(15)
T1HG	38	(36)
T1HG+CIS	17	(16)
TaHG	22	(21)
TaHG+CIS	14	(13)
Pre-Gem/Doce CIS-containing (%):		
No	60	(56)
Yes	47	(44)
No. full treatments in first induction (%):		
1	1	(0.9)
3	2	(1.9)
4	1	(0.9)
5	3	(2.8)
6	100	(94)
No. received maintenance (%):		
No	22	(21)
Yes	85	(79)

* These reports both included 1 missing data response.

Table 2. *Adverse events reported in patients treated with sequential Gem/Doce*

	Grade 1	Grade 2	Grade 3	Grade 4-5
Total reported adverse events (%)	31 (34)	60 (65)	1 (1.1)	0
No. specific events (%):				
Dysuria	4 (4.3)	6 (6.5)	-	-
Hematuria	4 (4.3)	12 (13)	-	-
Urinary frequency/urgency	7 (7.6)	39 (42)	-	-
Urinary retention	5 (5.4)	-	-	-
Nausea	3 (3.3)	-	-	-
Fatigue	5 (5.4)	-	-	-
Rash/skin irritation	-	2 (2.2)	-	-
Atrial fibrillation	-	-	1 (1.1)	-
Vasovagal syncope	-	1 (1.1)	-	-
Bladder/flank pain	3 (3.3)	-	-	-
No. pts reporting adverse events (%)	60 (56)			
No. full induction not received due to intolerance (%)	4 (3.7)			
No side effects affected treatment schedule (%)	9 (8.4)			

Adverse events are assigned according to CTCAE v5. Percentages of adverse events correspond to number/total instances of reported adverse events (92).

RFS

Median followup for survival was 15 months (IQR: 8–26). There were 19 (17.8%) patients with bladder cancer recurrence during followup. At time of first recurrence, stage of recurrence was 10 (53%) CIS, 1 (5.3%) HGT1, 5 (26%) HGTa and 1 (5.3%) HGTa+CIS, 2 (11%) LGTa. The majority of first recurrences had a component of CIS present (58%). At time of first recurrence, there was no stage progression from CIS/Ta to T1 or muscle-invasive disease. RFS was 89%, 85% and 82% at 6, 12 and 24 months, respectively (Fig. 1). The HG RFS was 91%, 87% and 84% at 6, 12 and 24 months, respectively (supplementary Fig. 1, https://www.jurology.com). RFS was similar for patients with CIS and non-CIS–containing disease (p=0.42; Fig. 2). Those with and without CIS-containing disease showed 77% and 86% RFS rates at 24 months, respectively. Among those who were disease-free at initial surveillance, DOR was 91% at 2 years (Fig. 3). There were 20 patients who received treatment for upper tract disease either prior to or during their bladder cancer treatment within this study. Considering the 7 patients with variant histology, 2 recurrences occurred within this group, 1 LGTa and 1 HGTa+CIS.

Progression and Survival

One patient underwent cystectomy due to end-stage lower urinary tract symptoms and recurrent CIS. Bladder capacity was measured as 140 cc prior to Gem/Doce therapy and approximately 40–50 cc prior to cystectomy. This patient was unable to tolerate more than 2 instillations of Gem/Doce and was switched to single-agent docetaxel prior to recurring on subsequent surveillance. Final pathology reported as pTisN0. There were no patients who developed metastatic disease or died of bladder cancer during the study period. OS was 84% at 24 months (Fig. 4).

Sensitivity Analyses

We performed a sensitivity analysis to assess for potential selection bias due to changing Gem/Doce utilization over time. Upon stratification of

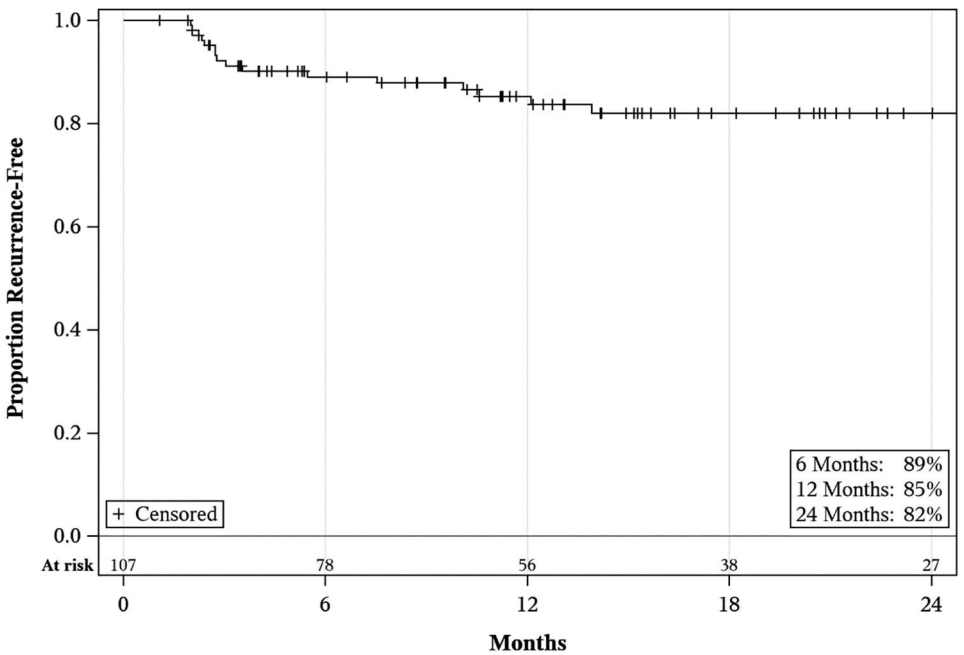

Figure 1. RFS following Gem/Doce induction.

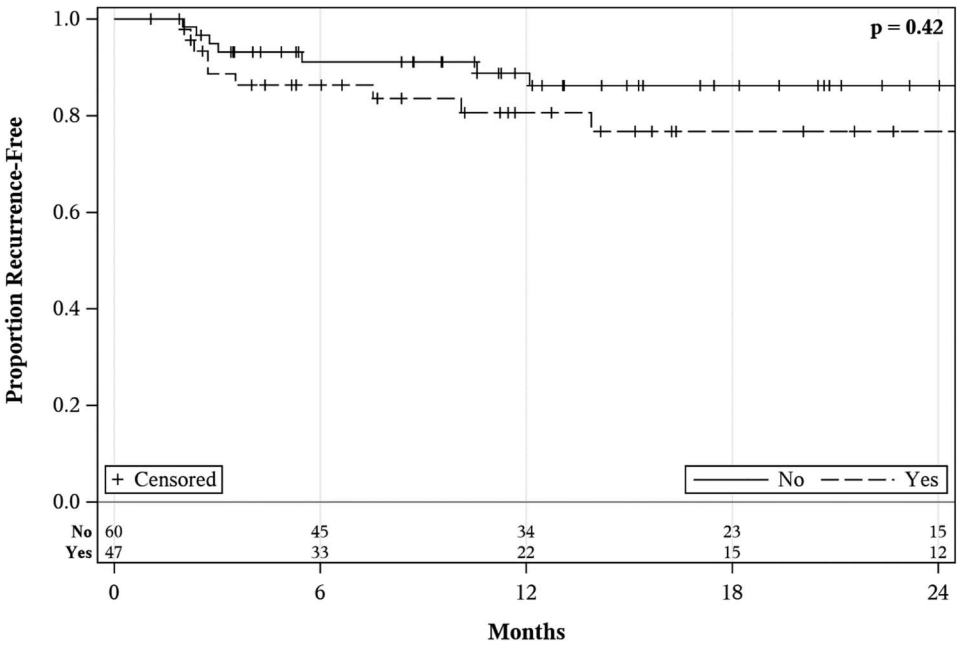

Figure 2. RFS stratified by CIS-containing disease.

analysis by receipt of Gem/Doce before 2019 and afterward, we found that RFS was not significantly different between groups (p = 0.44; supplementary Fig. 2, https://www.jurology.com). Furthermore, we identified 131 patients who received BCG during the same time period (May 2013–April 2021). A comparison of baseline clinical features between the BCG and Gem/Doce groups did not demonstrate statistically significant differences with respect to age (median 76 vs 76, p = 0.65), gender (79% vs 84% male, p = 0.35), race (96% vs 96% White, p = 1.0) or smoking status (33% vs 30% never-smoker, p = 0.56). In addition, the distribution of pathology at initial presentation was similar between the 2 treatment groups (p = 0.76) and with respect to CIS-containing

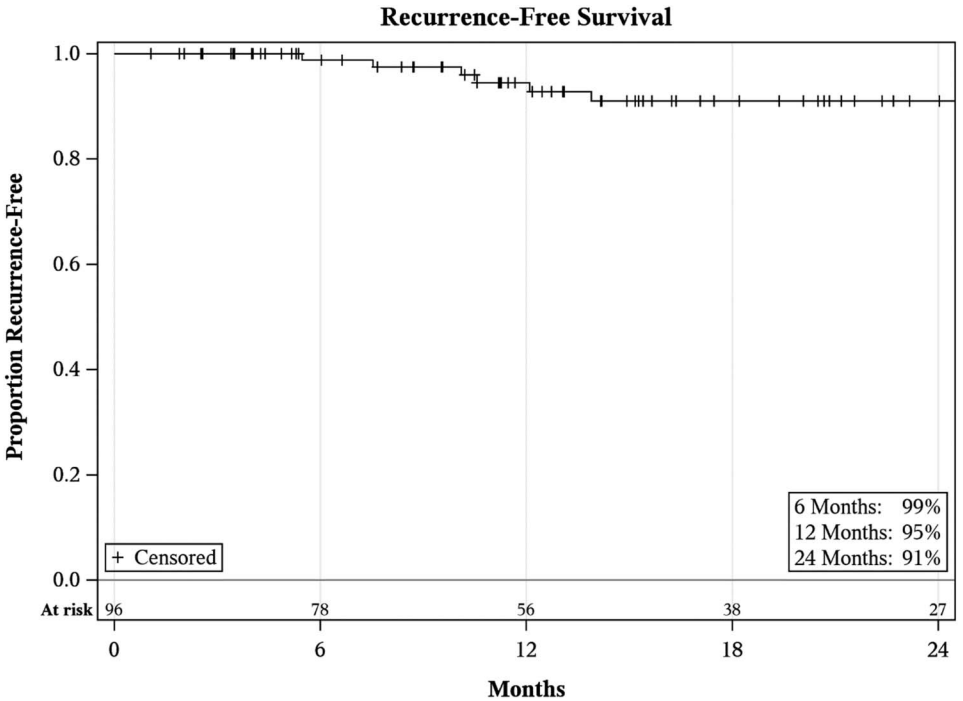

Figure 3. DOR among patients disease-free at initial surveillance.

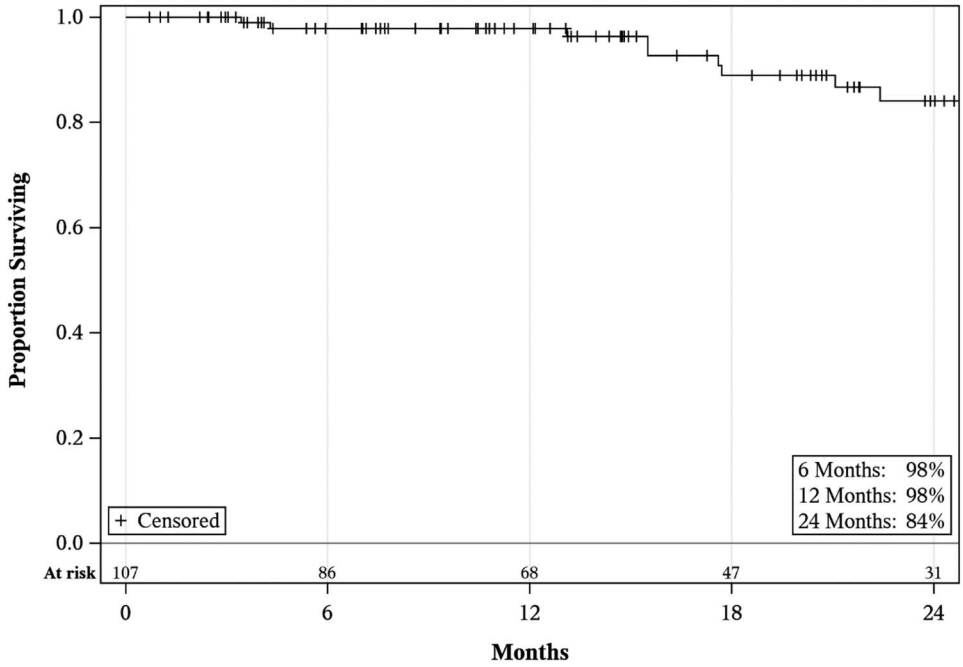

Figure 4. OS.

pathology (43% vs 44%, p=0.86). The large majority of patients reported here were treated with Gem/Doce in 2019 and 2020 (see supplementary Table, https://www.jurology.com). BCG usage rates had already declined in the wake of production shortages. However, when available, BCG was variably offered by some providers in our practice, complicating the ability to completely rule out selection bias.

DISCUSSION

Since its initial use in 1972, BCG has become the gold standard adjuvant treatment for high-risk NMIBC.[2,3] However, the ongoing BCG shortage has forced many urological practices to reevaluate alternative regimens. Our institutional experience with Gem/Doce in a high-risk BCG-naïve patient cohort, including a relatively unselected heterogeneous population, demonstrated an excellent 2-year HG RFS of 84%. While no direct comparator arm is present in this study, this rate is similar to those reported in modern BCG cohorts (~85%).[14–17] No patients developed progressive or metastatic disease even with >50% of patients with T1 disease prior to treatment. Finally, as previously demonstrated, Gem/Doce was very well tolerated with minimal treatment schedule alterations required.[9–11]

BCG induction with maintenance is associated with a decreased risk of bladder cancer recurrence and progression, and has demonstrated equivalent or superior efficacy over single-agent chemotherapy regimens.[17–19] Furthermore, the combination of chemotherapeutics in addition to BCG has not been shown to produce the same efficacy as BCG alone.[19] The role of combination multiagent chemotherapy is well established for systemic use in nearly all malignancies and provides compelling rationale for its use in the intravesical space. There exist a variety of new multiagent intravesical therapies that have been developed and tested in recent years.[20] Gem/Doce comprises well-tolerated antineoplastic agents that have demonstrated activity against bladder cancer when used in single-agent regimens.[21–24] Cellular uptake of gemcitabine prevents further DNA synthesis and ultimately results in apoptotic cell death.[25] Docetaxel opposes normal tubulin function and results in the inhibition of cell mitosis.[26] There is a likely synergistic effect of sequential utilization of agents, as a result of exfoliative effects of gemcitabine which allows improved permeability of taxane agents.[27]

To our knowledge, this is the largest report to date of BCG-naïve patients treated with Gem/Doce. Our results corroborate those of Babajide et al, who identified 78% 6-month RFS in a small series of 18 BCG-naïve patients with HG NMIBC.[12] In the 18-patient cohort, 2 recurrences were noted, with persistent T1 disease in 1 patient and stage progression from Ta to T1 disease in another. Our series demonstrated no stage progression, despite an exclusively high-risk population that included 7% patients with micropapillary variant histology.

Importantly, efficacy of BCG appears to be improving in modern cohorts, which may be secondary

to the increased utilization of blue light cystoscopy, improved resection techniques, and standardized risk-stratification and surveillance protocols.[14] For example, the control arm using standard BCG dosing in the NIMBUS trial demonstrated 85% 2-year RFS.[28] Matulay et al also assessed contemporary outcomes following adequate BCG in 421 patients with high-risk NMIBC and reported 79% 1-year RFS.[14] Thus, it appears that the 84% 2-year RFS observed in our study with Gem/Doce is similar to both contemporary retrospective and prospective outcomes of BCG.

There are limitations to our study. First, the retrospective nature allows for selection bias and confounding. The study is limited by the lack of a direct comparator group and selection bias was possible, as discussed above. The results are from a single high-volume institution with rigorous NMIBC protocols that may not be replicable in lower volume centers. This study was limited by relatively short followup. Although reported here, the retrospective design limited full confidence in classification of adverse events per CTCAE criteria. However, despite these limitations, in the setting of BCG shortage, these results support future well-designed, multiarm, prospective trials that may confirm the utility of first-line Gem/Doce for high-risk NMIBC.

CONCLUSIONS

We found that use of Gem/Doce for patients with high-risk, BCG-naïve NMIBC resulted in 84% 2-year HG RFS and a favorable tolerability profile. In the context of ongoing BCG shortage, our results highlight an effective and readily available alternative treatment in this patient population. These findings may serve as a benchmark for future prospective trial design assessing Gem/Doce as a first-line treatment for NMIBC.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE et al: Cancer statistics, 2021. CA Cancer J Clin 2021; **71:** 7.
2. Chang SS, Boorjian SA, Chou R et al: Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016; **196:** 1021.
3. Sylvester RJ, Rodríguez O, Hernández V et al: European Association of Urology (EAU) prognostic factor risk groups for non-muscle-invasive bladder cancer (NMIBC) incorporating the WHO 2004/2016 and WHO 1973 classification systems for grade: an update from the EAU NMIBC guidelines panel. Eur Urol 2021; **79:** 480.
4. American Urological Association: BCG Shortage Notice. Available at https://www.auanet.org/practice-resources/bcg-info/bcg-shortage-notice. Accessed June 22, 2021.
5. Nepple KG, Lightfoot AJ, Rosevear HM et al: Bacillus Calmette-Guérin with or without interferon α-2b and megadose versus recommended daily allowance vitamins during induction and maintenance intravesical treatment of non-muscle invasive bladder cancer. J Urol 2010; **184:** 1915.
6. Macleod LC, Ngo TC and Gonzalgo ML: Complications of intravesical bacillus Calmette-Guérin. Can Urol Assoc J 2014; **8:** e540.
7. Lamm DL: Comparison of BCG with other intravesical agents. Urology 1991; **37:** 30.
8. Shelley MD, Wilt TJ, Court J et al: Intravesical bacillus Calmette-Guérin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. BJU Int 2004; **93:** 485.
9. Steinberg RL, Thomas LJ, O'Donnell MA et al: Sequential intravesical gemcitabine and docetaxel for the salvage treatment of non-muscle invasive bladder cancer. Bladder Cancer Amst Neth 2015; **1:** 65.
10. Steinberg RL, Thomas LJ, Brooks N et al: Multi-institution evaluation of sequential gemcitabine and docetaxel as rescue therapy for nonmuscle invasive bladder cancer. J Urol 2020; **203:** 902.
11. Thomas L, Steinberg R, Nepple KG et al: Sequential intravesical gemcitabine and docetaxel in the treatment of BCG-naive patients with non-muscle invasive bladder cancer. J Clin Oncol 2019; **37:** 469.
12. Babajide R, Labbate C, Saoud R et al: Early experience with intravesical gemcitabine-docetaxel for BCG-naïve patients with high grade non-muscle invasive bladder cancer. Urol Oncol Semin Orig Investig 2020; **38:** 901.
13. Lamm D, Persad R, Brausi R et al: Defining progression in nonmuscle invasive bladder cancer: it is time for a new, standard definition. J Urol 2014; **191:** 20.
14. Matulay JT, Li R, Hensley PJ et al: Contemporary outcomes of patients with nonmuscle-invasive bladder cancer treated with bacillus Calmette-Guérin: implications for clinical trial design. J Urol 2021; **205:** 1612.
15. Lamm DL, Thor DE, Harris SC et al: Bacillus Calmette-Guerin immunotherapy of superficial bladder cancer. J Urol 1980; **124:** 38.
16. Lamm DL: Long-term results of intravesical therapy for superficial bladder cancer. Urol Clin North Am 1992; **19:** 573.
17. Lamm DL, Blumenstein BA, Crissman JD et al: Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000; **163:** 1124.
18. Oddens J, Brausi M, Sylvester R et al: Final results of an EORTC-GU Cancers Group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol 2013; **63:** 462.
19. Chou R, Selph S, Buckley DI et al: Intravesical therapy for the treatment of nonmuscle invasive bladder cancer: a systematic review and meta-analysis. J Urol 2017; **197:** 1189.
20. Steinberg RL, Thomas LJ and O'Donnell MA: Combination intravesical chemotherapy for non—muscle-invasive bladder cancer. Eur Urol Focus 2018; **4:** 503.
21. Skinner EC, Goldman B, Sakr WA et al: SWOG S0353: phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical bacillus Calmette-Guérin. J Urol 2013; **190:** 1200.
22. Schlack K, Boegemann M, Steinestel J et al: The safety and efficacy of gemcitabine for the treatment of bladder cancer. Expert Rev Anticancer Ther 2016; **16:** 255.
23. de Wit R, Kruit WH, Stoter G et al: Docetaxel (taxotere): an active agent in metastatic urothelial cancer; results of a phase 11 study in non-chemotherapy-pretreated patients. Br J Cancer 1998; **78:** 1342.

24. Barlow LJ, McKiernan JM and Benson MC: Long-term survival outcomes with intravesical docetaxel for recurrent nonmuscle invasive bladder cancer after previous bacillus Calmette-Guérin therapy. J Urol 2013; **189:** 834.

25. Lilly E: GEMZAR (gemcitabine) injection, for intravenous use. Prescribing information. Available at http://pi.lilly.com/us/gemzar.pdf. Accessed October 31, 2021.

26. Sanofi: TAXOTERE® (docetaxel) injection, for intravenous use. Prescribing information. Available at https://products.sanofi.us/Taxotere/taxotere.html. Accessed July 7, 2021.

27. Pandey R, Jackson JK, Liggins R et al: Enhanced taxane uptake into bladder tissues following co-administration with either mitomycin C, doxorubicin or gemcitabine: association to exfoliation processes. BJU Int 2018; **122:** 898.

28. Grimm M-O, van der Heijden AG, Colombel M et al: Treatment of high-grade non-muscle-invasive bladder carcinoma by standard number and dose of BCG instillations versus reduced number and standard dose of BCG instillations: results of the European Association of Urology Research Foundation randomised phase III clinical trial "NIMBUS". Eur Urol 2020; **78:** 690.

EDITORIAL COMMENTS

For the intravesical treatment of nonmuscle-invasive bladder cancer (NMIBC), the sequential chemotherapy doublet of gemcitabine and docetaxel (Gem/Doce) is quite powerful. Compelling retrospective data have resulted in the widespread adoption of Gem/Doce for patients with NMIBC as salvage therapy after prior bacillus Calmette-Guérin (BCG)[1,2] when radical cystectomy or clinical trials are not available or advisable.[3] Such studies have further demonstrated that Gem/Doce is extremely safe and well tolerated.[1,2]

The manufacturing shortage of BCG for intravesical therapy in patients with high-risk NMIBC poses a substantial challenge for urologists and patients, and this challenge may persist in the long term. Therefore, it is a priority to study the extent to which intravesical Gem/Doce might also be effective as a first-line therapy for patients with high-risk NMIBC.

McElree et al report retrospective outcomes from a single center that treated a large cohort of patients with Gem/Doce rather than BCG as first-line treatment for high-risk NMIBC. Recurrence-free survival at 2 years was about 80%, which is extremely encouraging and comparable to results from BCG first-line therapy from well-studied cohorts such as SWOG-8507. Of note, recurrence-free survival did not differ based on whether a patient harbored carcinoma *in situ* at baseline.

Though limited by retrospective design and absence of a comparison cohort, this study nevertheless presents a compelling justification for prospective trials (such as NCT04386746) to confirm these results. Meanwhile, these findings are highly impactful as patients and their treating physicians should be reassured that Gem/Doce is a viable treatment option for high-risk NMIBC in the frontline setting, especially if BCG is not available or contraindicated. We would like to congratulate the bladder cancer research team at the University of Iowa for a magnificent body of work on Gem/Doce that will benefit patient care for years to come.

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REFERENCES

1. Steinberg RL, Thomas LJ, Brooks N et al: Multi-institution evaluation of sequential gemcitabine and docetaxel as rescue therapy for non-muscle invasive bladder cancer. J Urol 2020; **203:** 902.

2. Milbar N, Kates M, Chappidi MR et al: Oncological outcomes of sequential intravesical gemcitabine and docetaxel in patients with non-muscle invasive bladder cancer. Bladder Cancer 2017; **3:** 293.

3. Roumiguié M and Black PC: Sequential gemcitabine plus docetaxel is the standard second-line intravesical therapy for BCG-unresponsive non-muscle-invasive bladder cancer: pro. Eur Urol Focus 2021; https://doi.org/10.1016/j.euf.2021.07.018.

In the era of frequent bacillus Calmette-Guérin (BCG) shortages, the American Urological Association and the Society of Urologic Oncology recommend prioritizing induction courses over maintenance courses of BCG.[1] Frequently, however, there may not be sufficient BCG supply for even induction courses. In such situations, clinicians often resort to intravesical chemotherapy regimens, such as single-agent mitomycin, to provide some degree of oncologic control.

In the current study, McElree et al retrospectively reviewed 107 BCG-naïve high-risk nonmuscle-invasive bladder cancer (NMIBC) patients receiving induction intravesical gemcitabine-docetaxel for 6

weeks followed by monthly maintenance up to 2 years (received by 79% of patients). With a median followup of 15 months, the 2-year recurrence-free survival was 82%, and no muscle-invasive or metastatic progressions were found. Patients without evidence of disease at first surveillance had a 91% chance of remaining free of disease at 2 years. Although 56% had adverse events, nearly all were grade 1-2, and 97% were able to complete at least 5 induction doses.

The authors should be commended for providing hypothesis-generating retrospective data for an alternative induction therapy to BCG for high-risk NMIBC. This complements the recent retrospective multi-institutional series supporting the efficacy of the same gemcitabine-docetaxel regimen in the BCG-unresponsive space.[2] Ideally, these data should be used to conduct a randomized trial of gemcitabine-docetaxel vs BCG for BCG-naïve high-risk NMIBC. Such a design would help overcome many of the limitations inherent to the present retrospective, single-arm study. If such a trial is not feasible, then a large multi-institutional series with a BCG comparator arm to enable multivariable statistical adjustments would also serve to allay some shortcomings of the present series. Provided such studies confirm its efficacy and tolerability, gemcitabine-docetaxel's supply chain advantages may be reason enough to supplant BCG as the initial treatment of choice for high-risk NMIBC.

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REFERENCES

1. American Urological Association: BCG Shortage Notice. Available at https://www.auanet.org/practice-resources/bcg-info/bcg-shortage-notice. Accessed May 1, 2022.
2. Steinberg RL, Thomas LJ, Brooks N et al: Multi-institution evaluation of sequential gemcitabine and docetaxel as rescue therapy for nonmuscle invasive bladder cancer. J Urol 2020; **203:** 902.

High-risk nonmuscle-invasive bladder cancer (NMIBC), characterized by high rates of recurrence and progression, poses a unique treatment challenge. In this high-risk population, urologists try to optimize oncologic control, while sparing patients the morbidity of radical cystectomy. Current guidelines recommend complete transurethral resection, followed by intravesical bacillus Calmette-Guérin (BCG). However, BCG's suboptimal efficacy and tolerability remain crucial limitations, only exacerbated by the continued BCG shortage.

Investigators have studied several monotherapy regimens—gemcitabine, mitomycin C and docetaxel—as alternatives to BCG. However, prospective studies have not demonstrated durable efficacy beyond 1 or 2 years.[1] In BCG-unresponsive NMIBC, pembrolizumab monotherapy has demonstrated moderate oncologic efficacy. Despite marginable durability, pembrolizumab gained U.S. Food and Drug Administration approval following publication of KEYNOTE-057.[2]

Given prior studies examining monotherapy regimens, more recent work has studied doublet therapies. For example, in a larger retrospective multi-institutional study, combination gemcitabine-docetaxel therapy has demonstrated encouraging results with 52% 2-year high grade recurrence-free survival for patients requiring salvage therapy after BCG failure.[3]

This well-presented article by McElree et al exists at the confluence of these prior data. The authors detail an institutional series of 107 patients with BCG-naïve high-risk NMIBC receiving sequential intravesical gemcitabine and docetaxel. With regular surveillance, including cystoscopy and upper tract imaging, patients had recurrence-free survival of 82% at 2 years (median followup 15 months [IQR: 8–26]). These survival rates are similar to the standard-of-care BCG regimens as reported in prior trials. We commend the authors, not only for reporting the largest series of gemcitabine-docetaxel in BCG-naïve bladder cancer, but also for doing so with granular institutional data. Though retrospective, this manuscript represents an important effort to find solutions in the BCG shortage era and offer efficacious, well-tolerated treatment regimens for NMIBC. Furthermore, it provides a new treatment option and a platform for prospective trials to bolster the treatment paradigm in bladder cancer.

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REFERENCES

1. Yassaie O, Chehroudi C and Black PC: Novel and emerging approaches in the management of non-muscle invasive urothelial carcinoma. Ther Adv Med Oncol 2021; **13:** 17588359211039052.
2. Balar AV, Kamat AM, Kulkarni GS et al: Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. Lancet Oncol 2021; **22:** 919.
3. Steinberg RL, Thomas LJ, Brooks N et al: Multi-institution evaluation of sequential gemcitabine and docetaxel as rescue therapy for non-muscle invasive bladder cancer. J Urol 2020; **203:** 902.

REPLY BY AUTHORS

Sequential intravesical gemcitabine and docetaxel (Gem/Doce) has been widely adopted since its initial description by our group in 2015.[1] While first utilized for patients with high-risk nonmuscle-invasive bladder cancer in whom bacillus Calmette-Guérin (BCG) failed, the now chronic BCG shortage has forced the hand of many urologists to utilize alternative primarily chemotherapeutic intravesical induction regimens, which occurred over time in our practice. Our retrospective series has demonstrated that this multiagent regimen has oncologic efficacy on par with BCG, in contrast to chemotherapy monotherapy, which has been shown to be suboptimal in prior randomized trials.

We completely agree that the next logical step is prospective validation and ideally randomized comparison to BCG. There is an ongoing phase I trial (NCT04386746) with promising preliminary results. Furthermore, we have a phase II trial assessing efficacy along with several pilot biomarker studies that are attempting to discover predictors for response. In the setting of BCG shortage, we are working to identify effective salvage regimens for patients who are "docetaxel unresponsive," and have found promising results exploring sequential valrubicin- and cabazitaxel-containing regimens.[2,3] Finally, there are plans for a phase III randomized trial of Gem/Doce and BCG that is likely activating in the near future.

While we enthusiastically take part in these prospective efforts, the fact remains that there are persistently severe supply shortages for BCG in the real world. These shortages appear to fluctuate over time and have differing impact based on institution as well as regionally throughout the United States. In this context, Gem/Doce has proven to be a readily available and effective alternative treatment option for patients, and for that we are grateful.

REFERENCES

1. Steinberg RL, Thomas LJ, O'Donnell MA et al: Sequential intravesical gemcitabine and docetaxel for the salvage treatment of non-muscle invasive bladder cancer. Bladder Cancer 2015; **1:** 65.
2. McElree IM, Packiam VT, Steinberg RL et al: Sequential intravesical valrubicin and docetaxel for the treatment of nonmuscle invasive bladder cancer. J Clin Oncol 2022; **40:** 496.
3. Packiam VT, McElree I, Steinberg RL et al: PD26-07 Sequential endoluminal cabazitaxel and gemcitabine with pembrolizumab for docetaxel-unresponsive non-muscle invasive urothelial carcinoma of the upper and lower urinary tracts. J Urol, suppl., 2022; **207:** e489.