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REVIEW

Sequential Intravesical Gemcitabine and Docetaxel for Non-Muscle Invasive Bladder Cancer: A Narrative Review Across Risk Groups

Mahdi Hemmati Ghavshough, Melinda Z Fu, Raeesa Islam, Disha Patel, Saum Ghodoussipour, Vignesh T Packiam

Department of Urology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA

Correspondence: Vignesh T Packiam, Department of Urology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA, Tel +1 (203) 510-3442, Email vp624@cinj.rutgers.edu

Background: Non–muscle-invasive bladder cancer (NMIBC) accounts for the majority of newly diagnosed bladder cancer cases and is characterized by high rates of recurrence and progression. Intravesical Bacillus Calmette–Guérin (BCG) remains the standard of care for high-risk disease; however, treatment intolerance, failure, and global supply shortages have prompted investigation of alternative intravesical therapies.

Objective: To summarize and critically appraise the existing clinical evidence evaluating sequential intravesical gemcitabine and docetaxel (Gem/Doce) in NMIBC, across different clinical contexts.

Methods: We performed a narrative review of published clinical studies assessing sequential intravesical Gem/Doce in patients with BCG-unresponsive, BCG-exposed, and selected treatment-naïve NMIBC. Reported oncologic outcomes, including recurrence-free survival, progression, cystectomy rates, and treatment-related adverse events, were reviewed. Emerging exploratory approaches, including biomarker-based risk stratification, were also described.

Results: Across multiple retrospective and prospective studies, Gem/Doce has demonstrates favorable recurrence-free survival, and acceptable safety profiles, particularly in patients with BCG-unresponsive or previously treated high-risk NMIBC. Reported rates of progression and cystectomy are generally low, and treatment discontinuation due to toxicity is uncommon. Exploratory studies have evaluated AI-assisted histologic biomarkers as potential tools for risk stratification and hypothesis-generating treatment selection; however, these approaches remain investigational and require prospective validation.

Conclusion: Current evidence suggests that sequential intravesical Gem/Doce is a well-tolerated bladder-sparing option with encouraging oncologic outcomes, particularly in patients with recurrent or BCG-unresponsive NMIBC. While early data have explored its use in treatment-naïve settings, definitive conclusions regarding its role as first-line therapy require validation in prospective randomized trials.

Keywords: urinary bladder neoplasms, gemcitabine, docetaxel, refractory, treatment failure, naïve, untreated

Introduction

Epidemiology and Global Burden

Bladder cancer represents a major global health burden, with approximately 550,000 new cases diagnosed annually worldwide and a marked male predominance.[1] In Western countries, it remains among the most frequently diagnosed malignancies, with an estimated 84,870 new cases and 16,540 disease-related deaths projected in the United States in 2025.[2]

At initial diagnosis, more than 70% of patients present with non–muscle-invasive bladder cancer (NMIBC).[3] NMIBC comprises a biologically and clinically heterogeneous group of tumors, including noninvasive papillary disease (Ta), lamina propria–invasive tumors (T1), and carcinoma in situ (CIS). Although cancer-specific survival is generally

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favorable, NMIBC is characterized by high rates of recurrence and a variable risk of progression, necessitating long-term surveillance and repeated interventions that contribute substantially to healthcare utilization and cost.[4]

Management of NMIBC is guided by tumor stage, grade, and risk stratification. Low-risk disease, typically Ta tumors, is managed with transurethral resection followed by a single immediate postoperative instillation of intravesical chemotherapy.[5] Patients with intermediate-risk NMIBC may receive induction intravesical chemotherapy or bacillus Calmette–Guérin (BCG), depending on individual risk features.[5] High-risk NMIBC—including T1 tumors and CIS—is preferentially treated with intravesical BCG with maintenance therapy.[5]

Despite its long-standing role as standard therapy for high-risk NMIBC over the past four decades, BCG failure remains common. A substantial proportion of patients experience disease recurrence or progression despite adequate BCG exposure, placing them at increased risk for progression to muscle-invasive disease. In patients with BCG-unresponsive high-risk NMIBC, early radical cystectomy remains the guideline-recommended definitive treatment, while bladder-sparing alternatives—including intravesical chemotherapy, systemic immunotherapy, and gene-based approaches—may be considered in carefully selected patients who are unwilling or unfit for surgery.[5]

Current Standard of Care for NMIBC

Transurethral Resection Of Bladder Tumor (TURBT)

TURBT remains the standard initial treatment for NMIBC, serving both diagnostic and therapeutic purposes by providing tissue for histopathologic evaluation while removing visible tumor.[6] In most cases, TURBT is followed by adjuvant intravesical therapy, with treatment selection guided by tumor stage, grade, and individual risk stratification.

For patients with low-risk NMIBC, a single immediate postoperative instillation of intravesical chemotherapy—most commonly gemcitabine or mitomycin C—has been shown to reduce recurrence and is recommended in contemporary guidelines.[7,8] In contrast, patients with high-risk disease often require additional interventions beyond initial resection.[9]

Repeat TURBT plays a critical diagnostic, prognostic, and therapeutic role in high-risk NMIBC, particularly in patients with T1 tumors, high-volume or high-grade Ta disease, or when the initial resection is incomplete or lacks muscularis propria. Repeat resection improves staging accuracy, facilitates detection of residual disease, and reduces the risk of early recurrence.[9,10] Although a subset of patients may achieve adequate disease control with re-resection alone, those with carcinoma in situ, multifocal tumors, or recurrent disease typically require further intravesical therapy.

In select cases, the decision to forgo repeat TURBT may be individualized based on clinical judgment and patient-specific factors. Overall, repeat TURBT remains a key component of risk stratification and informs subsequent management decisions, including intravesical bacillus Calmette–Guérin therapy or consideration of early radical cystectomy in appropriately selected patients.[9,10]

BCG Therapy

Historical Perspective and Mechanism of Action

BCG was developed in the early twentieth century as a vaccine against tuberculosis, and its antitumor potential was recognized in the 1970s following observations of immune-mediated tumor suppression.[11] The first clinical application of intravesical BCG in bladder cancer was reported in 1976, demonstrating durable responses in patients with non–muscle-invasive disease.[12]

Since that time, BCG has remained the standard adjuvant intravesical therapy for intermediate- and high-risk NMIBC, as endorsed by major international guidelines.[13] Multiple randomized and prospective studies have demonstrated that BCG reduces recurrence and progression and improves disease-specific outcomes compared with single-agent intravesical chemotherapy.[14–16]

The antitumor activity of BCG is primarily mediated through immune activation within the bladder microenvironment. Following intravesical instillation, BCG adheres to urothelial cells and triggers a local inflammatory response, resulting in recruitment of innate and adaptive immune cells and release of cytokines that promote tumor cell death. The degree of immune activation appears to correlate with therapeutic efficacy, although this response is also responsible for many treatment-related symptoms.[17]

Clinical Limitation of BCG

Despite its long-standing role and established immunologic efficacy, several limitations restrict the widespread use of intravesical BCG in NMIBC management, including global supply constraints, treatment-related toxicity, and a substantial rate of treatment failure leading to BCG-unresponsive disease.

Global BCG Shortage

A persistent worldwide shortage of BCG, largely driven by manufacturing constraints, has significantly limited its availability.[18] To optimize allocation, professional societies such as the Society of Urologic Oncology and the American Urological Association recommend prioritizing BCG for patients at highest risk of disease progression, while alternative intravesical agents are advised for intermediate- or lower-risk disease.[19,20] This shortage remains a major barrier to equitable access, particularly in resource-limited settings.

Adverse Events and Tolerability

BCG therapy is frequently associated with adverse events, with over 70% of patients experiencing local or systemic symptoms and approximately 8% discontinuing treatment due to intolerance.[21,22] Common adverse effects include urinary frequency, dysuria, hematuria, irritative cystitis, and transient flu-like symptoms, which typically resolve within 48–72 hours.[19,23,24] Although less common, serious complications such as granulomatous infections, epididymo-orchitis, and disseminated BCG infection have been reported and may rarely be life-threatening, requiring prompt recognition and management.[4,25,26]

BCG Failure and Unresponsive Disease

Despite standard induction and maintenance regimens, treatment failure remains a significant limitation of BCG therapy.[27] Approximately 20–30% of patients experience primary BCG failure, and up to 40–50% of high-risk patients develop recurrent or progressive disease within 2–5 years.[28,29] Elderly and immunocompromised patients are particularly susceptible to treatment failure[30] and up to 10% of individuals with high-risk NMIBC ultimately progress to muscle-invasive disease despite adequate therapy.[31] BCG-unresponsive disease—defined by early recurrence of high-grade disease or persistent carcinoma in situ following adequate treatment—represents a major clinical challenge and underscores the need for effective bladder-sparing salvage strategies.[31]

Management of BCG-Unresponsive NMIBC

Radical Cystectomy (RC)

Early radical cystectomy (RC) with pelvic lymph node dissection remains the gold standard for patients with BCG-unresponsive NMIBC, as endorsed by both the EAU and AUA guidelines.[32] Patients with BCG-unresponsive disease face a considerable risk of progression to MIBC, metastatic spread, and disease-specific mortality, underscoring the importance of timely surgical intervention to optimize oncologic outcomes.

Multiple studies have demonstrated superior survival outcomes with early RC compared to delayed intervention. Immediate cystectomy has been associated with a 10-year cancer-specific survival (CSS) of 83%.[33] Patients undergoing RC within two years of BCG failure achieved a CSS of 92%, compared with 56% among those who delay surgery in a report from 2001,[34] highlighting the prognostic benefit of early surgical management. In a more contemporary analysis of 378 patients with high-grade NMIBC undergoing RC after BCG failure, Packiam et al[35] reported that prior salvage intravesical therapy did not increase the risk of adverse pathology or compromise CSS, suggesting that initial bladder-preserving attempts do not negatively impact surgical outcomes. Similarly, in 2025, Taylor et al[36] found that initial bladder-sparing therapy yielded survival outcomes comparable to upfront RC in a well-selected mutli-institional cohort.

RC is a major operation associated with substantial morbidity and long-term quality-of-life implications. Postoperative complications occur in up to 60% of patients, and perioperative mortality within 30 days is reported at approximately 1.5%.[37,38] Moreover, permanent loss of native bladder function and the need for urinary diversion can significantly impact physical, psychological, and social well-being. Consequently, many patients are reluctant to undergo

or tend to postpone surgery whenever feasible, highlighting the ongoing demand for effective and durable bladder-sparing alternatives.

Additional Courses of BCG

In clinical practice, some patients may undergo additional courses of BCG following initial treatment failure; however, repetitive inductions result in limited therapeutic benefit. Patients with recurrent relapses rarely achieve durable responses with further BCG exposure.[39] Reported outcomes indicate a two-year recurrence-free survival (RFS) rate of approximately 35% after a second induction course, with fewer than 20% achieving long-term remission beyond two courses.[32]

The likelihood of benefit decreases further among patients who relapse within two years of initial BCG therapy, with response rates falling below 30%.[40] Moreover, repeated BCG instillations are not without risk, as cumulative exposure has been associated with an increased probability of disease progression.[33] Nonetheless, selected patients may still derive clinical benefit. Myers et al[41] reported that in carefully chosen individuals meeting BCG-unresponsive criteria, a rescue BCG regimen achieved a two-year disease-free survival (DFS) rate of 63% and durable long-term control in 75% of cases, suggesting that additional BCG may remain effective in a subset of non-progressive disease. Likewise, Taylor et al[42] demonstrated that a second induction course in relapsing patients resulted in two-year RFS outcomes comparable to those achieved with several contemporary intravesical agents, indicating that repeat BCG continues to be a reasonable option in appropriately selected cases.

Collectively, these findings underscore the diminishing returns associated with additional BCG therapy and highlight the ongoing need for effective, well-tolerated salvage strategies for patients with recurrent or BCG-unresponsive NMIBC.

Alternative Intravesical and Systemic Therapies

Given the limitations of intravesical BCG, including treatment-related toxicity, global shortages, and variable efficacy, the development of bladder-sparing strategies for intermediate- and high-risk NMIBC has become a clinical priority.[3,22,43] A range of alternative approaches has been explored, including intravesical chemotherapy, systemic immunotherapy, and gene-based therapies, with combination intravesical regimens generally demonstrating greater efficacy than single-agent approaches.[44,45]

Currently, five agents are approved by the US Food and Drug Administration (FDA) for the treatment of high-risk NMIBC. Valrubicin, an intravesical anthracycline approved in 1998, was the first therapy for BCG-refractory carcinoma in situ, although it is rarely used due to 2 year CR of only 4%.[46] Pembrolizumab, a systemic PD-1 inhibitor, received approval following the KEYNOTE-057 trial, which reported a 19% 12-month complete response (CR) rate in patients with BCG-unresponsive carcinoma in situ.[47] Nadofaragene firadenovec, an intravesical adenoviral vector delivering interferon-α2b, achieved a 24% 12-month CR rate in patients with CIS in a pivotal Phase III trial.[48] More recently, N-803 (Anktiva) in combination with BCG demonstrated a 45% 12-month CR rate, which includes re-induction in some of the cohort.[49] Finally, TAR-200 (Inlexzo), a gemcitabine-releasing intravesical device, demonstrated 12-month CR of 46%, leading to recent FDA approval.[50]

Beyond these approved options, numerous investigational therapies are in active evaluation. Novel agents such as cretostimogene grenadenorepvec, detalimogene voraplasmid, and combination regimens incorporating gemcitabine or docetaxel have shown preliminary promise.[51] Other innovative drug-delivery platformsare also being explored to enhance intravesical drug penetration and therapeutic efficacy.[48]

Despite these advancements, widespread adoption of alternative therapies remains constrained by high cost, limited availability, and a lack of mature long-term outcomes data.[52] For example, one-year CR rates are approximately 24% with nadofaragene firadenovec and 19% with pembrolizumab, and both treatments impose substantial financial burdens.[53] Even newer-generation modalities such as N-803 and TAR-200 demonstrate one-year CR rates of only 45–46%, which remain modest compared with outcomes reported for sequential intravesical gemcitabine and docetaxel (Gem/Doce). Since its initial report in 2015, Gem/Doce has garnered increasing attention due to its favorable efficacy, tolerability, accessibility, and low cost.[54]

Collectively, these findings underscore the persistent need for safe, accessible, and durable bladder-sparing regimens for patients with BCG-unresponsive NMIBC—among which Gem/Doce continues to represent one of the most practical and promising therapeutic options.

History and Rationale for Multi-Agent Approach

Single-agent intravesical chemotherapy has long been used in the management of NMIBC; however, its efficacy in high-grade and treatment-refractory disease is limited. A comprehensive systematic review and meta-analysis demonstrated that BCG provides superior oncologic control—achieving lower recurrence and progression rates—compared with single-agent intravesical chemotherapies.[55] These limitations, together with the superior outcomes observed with multi-agent regimens in systemic oncology, prompted the development of combination intravesical strategies for NMIBC. Sequential therapy offers the potential to target distinct molecular pathways, increase cytotoxic synergy, and mitigate drug resistance. Early studies evaluating sequential intravesical gemcitabine and mitomycin C showed favorable efficacy and tolerability.[56–58] However, following a global mitomycin C shortage in 2009, a novel sequential regimen combining gemcitabine and docetaxel (Gem/Doce) was conceived as an alternative. The first clinical experience with Gem/Doce was published in 2015, marking the beginning of a therapeutic strategy that has since demonstrated encouraging oncologic and safety outcomes in both BCG-unresponsive and BCG-naïve NMIBC.[59]

Sequential Gemcitabine–Docetaxel

Among emerging bladder-preserving therapies, sequential intravesical Gem/Doce has gained increasing attention. This regimen combines favorable tolerability, broad accessibility, and encouraging efficacy, positioning it as a practical option for patients with BCG-unresponsive NMIBC.

Single-Agent Chemotherapy

Gemcitabine

Gemcitabine, a deoxycytidine analog, exerts antitumor activity by inhibiting DNA synthesis and inducing apoptosis in rapidly proliferating cells.[60] Initially developed for systemic treatment of metastatic solid tumors, gemcitabine demonstrated therapeutic potential in NMIBC, particularly among patients with BCG-unresponsive disease.[9,59] Its favorable safety profile and minimal systemic absorption have further supported its use intravesically.[61]

Early-phase studies of intravesical gemcitabine monotherapy reported modest efficacy, with Phase II trials demonstrating one-year RFS rates of approximately 28% in BCG-unresponsive patients.[62] In a phase III trial, Skinner et al reported one- and two-year RFS rates of 28% and 21%, respectively, in patients who failed at least two prior BCG courses.[63] Interestingly, Escano et al observed that patients receiving gemcitabine within a clinical trial setting experienced significantly worse RFS than those treated outside of a trial.[64]

Although long-term durability remains limited, single-agent gemcitabine's favorable tolerability and established activity provide a rational foundation for multi-agent or sequential chemotherapy approaches designed to enhance oncologic control.[65]

Docetaxel

Docetaxel, a semisynthetic taxane derivative, inhibits microtubular depolymerization, resulting in mitotic arrest and apoptosis in proliferating cells.[66] Originally developed for advanced breast, prostate, and urothelial cancers, docetaxel has also demonstrated antitumor activity in NMIBC.[67] Studies of intravesical docetaxel monotherapy have reported one- and three-year RFS rates of approximately 40% and 25%, respectively,[68] Another institutional series found a one-year RFS of 50% among patients with prior BCG failure and noted excellent response rates and intermediate-term disease control.[69]

Despite its favorable safety profile, docetaxel's relatively large molecular size may limit urothelial penetration and reduce therapeutic exposure—similar to pharmacokinetic challenges seen with paclitaxel.[70] To improve drug delivery, alternative strategies such as microparticle formulations and direct intramural injection have been explored, demonstrating encouraging preliminary results.[71]

While single-agent docetaxel yields modest long-term outcomes, its tolerability and complementary mechanism of action relative to gemcitabine provide a strong biological rationale for incorporation into sequential intravesical regimens aimed at improving durability of response in NMIBC.

Combination Chemotherapy

Gemcitabine and Docetaxel (Gem/Doce)

Sequential intravesical Gem/Doce has emerged as one of the most efficacious bladder-sparing regimens for BCG-unresponsive NMIBC. Both drugs are FDA-approved and widely available, enhancing the practicality and scalability of this therapy across diverse healthcare settings. The therapeutic rationale is grounded in complementary mechanisms of action: gemcitabine inhibits DNA synthesis and disrupts the bladder glycosaminoglycan layer, improving mucosal permeability and subsequent docetaxel uptake.[60] Administering gemcitabine first also facilitates DNA incorporation, augmenting the antimicrotubule effects of docetaxel and producing synergistic cytotoxicity.[72]

Among salvage intravesical therapies, Gem/Doce is the only regimen that consistently achieves one-year RFS rates exceeding 50% without the need for specialized delivery platforms such as thermotherapy, intravesical beads, or implantable drug-releasing devices.[24,42] Compared with BCG, sequential Gem/Doce has demonstrated superior RFS, lower discontinuation rates, and comparable oncologic outcomes in appropriately selected high-risk cohorts.[59]

Given its demonstrated efficacy, favorable tolerability, and broad accessibility, sequential Gem/Doce represents a practical and effective bladder-preserving alternative for patients who decline or are ineligible for RC. Its ease of administration and reproducible outcomes continue to redefine the therapeutic landscape of BCG-unresponsive NMIBC.

Dosing and Administration

The standard Gem/Doce protocol begins with sterile catheter placement and complete bladder drainage. Gemcitabine (1 g in 50 mL sterile water) is instilled intravesically and retained for 60–90 minutes. After drainage, docetaxel (40 mg diluted in 54 mL normal saline) is instilled and retained for an additional 1–2 hours.[72]

Several supportive measures are recommended to optimize tolerability. Patients typically take 1300 mg of oral sodium bicarbonate prior to treatment to alkalinize the urine and neutralize the acidic gemcitabine solution (pH ≈ 2.5), which reduces bladder irritation and nausea. For patients with sodium restrictions, potassium citrate may be substituted. Prophylactic ondansetron is optional. To minimize intravesical drug dilution, patients are also advised to avoid diuretics and restrict fluid and caffeine intake on treatment days.[72]

As with most intravesical therapies, Gem/Doce is generally initiated 3–6 weeks following TURBT. However, in carefully selected individuals, due to no concern for hematogenous dissemination, earlier administration may be considered.[73] Technical modifications, including gravity-assisted instillation, have also been adopted to improve comfort and enhance treatment tolerability.[74,75]

Clinical Outcomes of Gemcitabine–Docetaxel

BCG Unresponsive Disease

Sequential intravesical Gem/Doce was first introduced in 2015 as a salvage regimen for NMIBC refractory to prior treatments, at a time when effective alternatives to BCG were limited.[59] Since then, Gem/Doce has emerged as one of the most effective and well-tolerated bladder-sparing options for BCG-unresponsive disease, with consistently durable oncologic outcomes across multiple investigations.[13,76]

In the initial multicenter experience, Gem/Doce achieved 12- and 24-month RFS rates of 60% and 46%, respectively.[24] Among patients with high-grade disease—including those categorized as refractory, relapsing, or unresponsive to BCG—RFS rates reached 65% and 52% at 12 and 24 months, respectively.[24] In the 38% of patients with BCG-unresponsive CIS, RFS rates were 60% and 50% at 12 and 24 months, respectively.[24]

Subsequent studies have consistently reproduced these favorable findings. In a large multicenter retrospective analysis of 299 BCG-unresponsive patients treated with Gem/Doce at 15 US institutions, Yim et al[77] reported 12- and 24-month RFS rates of 60% and 46%, with corresponding two-year progression-free and cystectomy-free survival rates of 97% and 81%. Treatment discontinuation due to adverse events occurred in only 3% of patients, underscoring the regimen's favorable tolerability profile. Chevuru et al[78] similarly observed that 65% of patients remained free of high-grade recurrence at one year.

Comparable outcomes have also been reported internationally. Pijpers et al[79] demonstrated two-year RFS rates of up to 69% in high-risk NMIBC, while Tan et al[80] and Kawada et al[81] each documented two-year RFS rates approaching 70%, with high-grade RFS of approximately 51%.

Taken together, the totality of evidence highlights the ability of Gem/Doce to achieve sustained disease control in BCG-unresponsive NMIBC while maintaining excellent tolerability and bladder preservation. The reproducibility of these outcomes across diverse institutions reinforces its role as a safe, effective, and widely available salvage therapy (Table 1).

BCG Naïve Disease

Emerging evidence supports the use of Gem/Doce as a first-line intravesical option in BCG-naïve patients with intermediate- and high-risk NMIBC.[59,74] In a retrospective analysis by McElree et al[86] 80% of high-risk BCG-naïve patients remained disease-free at two years, with RFS rates of 82% in the overall high-risk cohort and 84% among those with high-grade disease. No cases of local progression or metastatic spread were observed during a median follow-up of 21.4 months (range, 1.9–52.7 months).

Prospective data further support this role. In a Phase II single-arm trial, Patel et al[83] treated 25 BCG-naïve high-risk patients with induction Gem/Doce. The 3-month complete response rate was 100%, and 12-month RFS was 92%. No patient progressed to muscle-invasive disease, underwent cystectomy, or developed metastatic recurrence.

Additional evidence is expected from the BRIDGE trial,[88] a randomized Phase III study directly comparing Gem/Doce with BCG as first-line therapy for intermediate- and high-risk NMIBC. The trial is designed to evaluate non-inferiority in RFS and treatment-related toxicity. Should Gem/Doce demonstrate comparable cancer control with improved tolerability and accessibility, it may establish a new front-line standard. Results from BRIDGE are eagerly anticipated and hold the potential to influence future guideline recommendations.

Precision-medicine strategies may further refine first-line treatment selection. Packiam et al[89] evaluated an artificial-intelligence-enhanced histologic biomarker (CHAI) in treatment-naïve high-grade NMIBC patients receiving either BCG or Gem/Doce. Among CHAI-positive patients, BCG was associated with inferior 24-month high-grade RFS (56%), whereas RFS after Gem/Doce remained high (90%). In contrast, among CHAI-negative patients, outcomes were comparable between therapies. These findings suggest that CHAI may predict poor response to BCG but not to Gem/Doce, introducing the possibility of biomarker-guided first-line therapy.

Taken together, current evidence suggests that sequential Gem/Doce is a promising primary intravesical approach in selected BCG-naïve patients, with early efficacy and favorable tolerability; however, its role as primary therapy remains investigational and requires confirmation in prospective randomized trials (Table 1).

BCG-Exposed High-Risk NMIBC

Patients with high-risk NMIBC who have previously received BCG but do not meet criteria for BCG-unresponsive disease are considered BCG-exposed. These individuals have completed an adequate BCG course but recur outside the time interval defining BCG-unresponsiveness or relapse after a disease-free period following induction or maintenance therapy. Because many of these patients retain partial responsiveness to intravesical treatment, bladder-preserving therapies remain appropriate.

In a multicenter comparative analysis, Steinberg et al evaluated Gem/Doce in patients with recurrent NMIBC after a single BCG induction and reported adjusted one-year RFS of 68% and two-year RFS of 46%, with efficacy comparable to BCG plus interferon.[13] Similarly, in a multicenter European cohort, Scilipoti et al[87] evaluated sequential Gem/Doce in BCG-treated high-risk NMIBC. At a median follow-up of 9 months, one-year DFS was 73%, high-grade DFS was 79%, and progression-free survival reached 95%. Similarly, Lim et al[90] compared Gem/Doce with BCG re-induction in patients with recurrent high-grade disease after prior BCG exposure and observed comparable recurrence at first post-treatment cystoscopy (20% vs 18%).

Collectively, these findings indicate that Gem/Doce is a promising bladder-sparing strategy for BCG-exposed high-risk patients, particularly when BCG is unavailable or poorly tolerated.

Table 1 Comparative Studies on the Efficacy and Adverse Events of Gem and Doce in Various BCG Treatment Types for NMIBC

Authors	Study Design	BCG Type	No. Patients		Mean Age (Years)	RFS				Tolerance				
			Naïve	Unresponsive		Median Follow Up (Months)	1 Year	2 Year	5 Year	Treatment Incompletion Rate	AEs			
											No. Events	Grade 1-2	Grade 3-4-5	Most Common Symptoms
Bakula[82]	Prospective	Naïve	52	0	52	12	80%	NA		NA				
Patel[83]			25		56	19.6	92%	NA		NA	28	82.2%	7.8%	Urinary frequency/ Hematuria
Pareek[84]			60		57.5	NA	NA			0	NA	100%	0	Dysuria, Bladder spasm
McElree[3]	Retrospective		77		70	26	84%	71%	NA	6.89%	39	97.4%	2.6%	Urinary Frequency/ Urgency
McElree[85]			107		76	15	85%	82%	NA	5%	82	98.9%	1.1%	Urinary Frequency/ Urgency
McElree[86]			312		73	23	83%	78%	NA	2.9%	87	52.2%	1.14%	Bladder Spasms
Taylor[42]		Unresponsive	0	299	73	39	26%	38%	59%	NA				
Yim[77]				102	72	18	63%	38%	NA	NA	143	NA		Urinary Frequency/ Urgency
Garneau[10]				35	78	21	71%	37%	NA	6%	18	NA		Urinary Frequency/ Urgency
Chevuru[78]				97	73	25	57%	44%	24%	0%	78	100%	0%	Bladder Spasms
Scilipoti[87]				75	71	NA				NA	49	83.67%	8%	Irritative LUTS
David[2]				83	73	18	71%	57%	NA	NA	NA	16.8%	0%	Dysuria, urgency and frequency
Milbar[27]		Unresponsive and Naïve	8	25	72	17.6	56%	42%	NA	3.3%	41	NA		LUTS

Abbreviations: RFS, Recurrence-Free Survival; GEM, Gemcitabine; DOCE, Docetaxel; BCG, Bacillus Calmette-Guérin; NMIBC, Non-Muscle Invasive Bladder Cancer; LUST, Lower urinary tract symptoms; NA, Not Available; AEs, Adverse events; TURBT, transurethral resection of bladder tumor; RC, radical cystectomy.

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Intermediate-Risk NMIBC

Evidence supporting sequential Gem/Doce in intermediate-risk (IR) NMIBC remains limited, as most publications have focused on high-risk or BCG-unresponsive disease. However, early institutional experiences suggest that Gem/Doce may offer meaningful bladder preservation with acceptable tolerability among IR patients who recur after first-line intravesical chemotherapy.

In a multi-institutional cohort, Tan et al compared Gem/Doce with BCG in 182 IR-NMIBC patients and observed similar RFS at two years (75% vs 70%), supporting Gem/Doce as an alternative adjuvant option.[80] Likewise, McElree et al evaluated Gem/Doce in 77 IR-NMIBC patients and reported a two-year RFS of 71%, with superior outcomes in treatment-naïve individuals (79%) compared with previously treated patients (64%).[3]

Eraky et al[91] analyzed IR-NMIBC patients treated with either BCG or Gem/Doce and reported a two-year any-grade RFS of 55% at a median follow-up of 31 months. Stratified by tumor grade, two-year any-grade RFS was 58% for high-grade and 35% for low-grade disease. The authors suggested that BCG may provide superior high-grade RFS in patients with high-grade IR-NMIBC, whereas outcomes for low-grade tumors were comparable between therapies.

Similarly, Kolanukuduru et al[92] studied 483 IR-NMIBC patients treated with BCG or Gem/Doce and observed two-year high-grade RFS rates of 81% and 61%, respectively, with corresponding any-grade RFS of 60% versus 41%. Importantly, receipt of maintenance therapy was associated with a reduced risk of recurrence.

Taken together, these findings suggest that while Gem/Doce may serve as a viable bladder-preserving option in select IR-NMIBC patients, BCG may retain an advantage for those with high-grade disease.

Tolerability and Safety Profile

Sequential intravesical Gem/Doce is generally well tolerated, with low rates of treatment discontinuation and minimal high-grade toxicity. In a recent multicenter prospective study, McElree et al reported that 96% of patients completed all six induction instillations, and only 3.9% discontinued therapy due to intolerance.[3] Overall, 38% of patients experienced any adverse event, nearly all of which were grade 1–2, with a single grade 3 event (1.3%) related to transient oxygen desaturation that resolved without sequelae.[3] The most common toxicities included urinary frequency or urgency (10%), bladder spasms (9%), urinary tract infection (5%), hematuria (4%), and fatigue (4%), all of which were self-limited and manageable with standard supportive care.[3]

Compared with BCG, Gem/Doce demonstrates improved compliance and a lower incidence of treatment-limiting toxicity.[86] Abou et al,[56] observed fewer adverse events and better adherence with Gem/Doce than with BCG, while Pareek et al[84] reported higher patient-reported quality-of-life scores and fewer severe complications among those receiving Gem/Doce. Although bladder spasms and mild nausea may occur more frequently, the overall safety profile remains favorable.

Taken together, these findings underscore the excellent tolerability and patient acceptability of Gem/Doce, supporting its role as a safe and effective bladder-sparing alternative for patients with BCG-unresponsive or BCG-naïve NMIBC.

Economic and Practical Considerations

Bladder cancer is one of the most expensive malignancies to manage, due in part to lifelong surveillance, repeated intravesical therapies, and the cost of surgical intervention.[93,94] In the United States, the average cost of RC alone is estimated at $33,202, with an additional $14,417 attributable to hospital readmissions.[95] This economic burden directly influences treatment decisions, with up to 18% of patients declining chemotherapy because of cost.[96] As a result, bladder-sparing strategies that reduce the need for RC and hospital utilization offer substantial financial value for both patients and healthcare systems.

Sequential intravesical Gem/Doce, composed entirely of widely available generic agents, represents a cost-effective and practical alternative to BCG.[97] In a Medicare-based Markov model, Bukavina et al[98] demonstrated that Gem/Doce achieved comparable quality-adjusted life-years (1.76 QALYs) to BCG while reducing two-year mean per-patient costs from $12,363 with BCG to $7090 with Gem/Doce. Recurrence rates were also lower (17.3% vs 28.5%), and fewer patients required cystectomy (2.9% vs 7.5%), further supporting the clinical and economic value of Gem/Doce.[98]

Myers et al[99] further reported that Gem/Doce maintains a highly favorable cost profile compared with FDA-approved therapies for BCG-unresponsive NMIBC, concluding that gemcitabine/docetaxel is the most cost-effective option when a single salvage therapy line is considered.

Future Directions

Although sequential Gem/Doce has demonstrated encouraging efficacy, tolerability, and real-world applicability, several key questions must be answered before it can be fully integrated into standard NMIBC management.

First, optimization of induction and maintenance schedules is needed to maximize therapeutic benefit while minimizing toxicity. The ideal number of instillations, treatment intervals, and duration of maintenance therapy remain undefined, and standardized protocols are required to ensure consistent outcomes across centers. Second, the long-term durability of oncologic control must be validated through extended follow-up in prospective, multicenter trials.

Future investigation should also prioritize biomarker-driven patient selection. Integration of molecular profiling, genomics, and immune-based signatures may identify patients most likely to benefit from Gem/Doce, enabling a personalized therapeutic approach and reducing unnecessary exposure for those unlikely to respond.

Finally, combination strategies incorporating Gem/Doce with emerging systemic or intravesical therapies—such as immune checkpoint inhibition, viral gene therapy, or novel drug-delivery platforms—hold potential to further enhance efficacy, particularly in high-risk or rapidly recurrent disease. As evidence continues to expand, sequential Gem/Doce may play an increasingly pivotal role in redefining bladder preservation strategies for both BCG-unresponsive and BCG-naïve NMIBC.

Recent high-impact reviews and guideline updates published in *European Urology* continue to support intravesical bacillus Calmette–Guérin as the standard first-line therapy for high-risk NMIBC and emphasize that alternative intravesical regimens should be considered investigational in the treatment-naïve setting pending randomized evidence. These conclusions are consistent with the cautious interpretation adopted in this review, particularly regarding emerging first-line applications of gemcitabine/docetaxel.[5]

Limitations and Evidence Gaps

Despite encouraging oncologic and tolerability outcomes, the current evidence supporting sequential intravesical gemcitabine and docetaxel has important limitations. Most available studies are retrospective and derived from single-center or high-volume tertiary institutional experiences, introducing potential selection bias and limiting generalizability. Patient populations are heterogeneous with respect to tumor risk, prior BCG exposure, and use of maintenance therapy, complicating direct comparison across studies. Long-term durability beyond five years remains incompletely characterized, and no completed randomized trials have yet compared Gem/Doce with guideline-recommended standards of care, although prospective studies are ongoing. In addition, economic analyses are largely model-based, and emerging biomarker or artificial intelligence–assisted treatment selection strategies remain exploratory. These gaps highlight the need for prospective, multicenter trials with standardized protocols and extended follow-up.

Conclusion

NMIBC remains a clinically challenging disease, particularly in patients with high-risk T1 and BCG-unresponsive tumors, who face substantial risks of recurrence and progression. Despite the long-standing role of intravesical BCG, its limitations—including treatment-related toxicity, global supply shortages, and a significant rate of treatment failure—highlight the ongoing need for effective bladder-sparing alternatives in selected patients.

Within this context, sequential intravesical gemcitabine and docetaxel has emerged as a well-tolerated and accessible option with encouraging oncologic outcomes, particularly in patients with BCG-unresponsive disease. Available evidence demonstrates favorable recurrence-free survival, acceptable safety profiles, and broad clinical applicability, supported by the use of widely available generic agents. These features distinguish Gem/Doce from several newer therapies that are associated with higher cost, limited availability, or modest durability of response.

While current data support the role of Gem/Doce as a bladder-preserving strategy in appropriately selected patients, its optimal positioning within NMIBC treatment algorithms continues to evolve. Prospective, multicenter studies with

long-term follow-up are needed to further define durability of response, refine treatment protocols, and clarify its role relative to established guideline-recommended therapies.

Data Sharing Statement

No datasets were generated or analyzed in this study. Data sharing is therefore not applicable.

Ethic Statement

This study is a narrative review of previously published literature and did not involve human participants, identifiable personal data, or animal subjects. Therefore, institutional review board approval and informed consent were not required.

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Disclosure

Vignesh Packiam reports personal fees from Valar Labs, personal fees from Veracyte, personal fees from Photocure, personal fees from Ferring, personal fees from Jannsen, personal fees from Urogen, outside the submitted work. The authors report no other conflicts of interest in this work.

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