ORIGINAL RESEARCH

Efficacy of Intravesical Gemcitabine and Docetaxel for Non-Muscle Invasive Urothelial Bladder Cancer: A Review of Current Literature

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Objective: To determine the efficacy of sequential intravesical Gemcitabine and Docetaxel (siGD) in patients with non-muscle invasive bladder cancer (NMIBC) in preventing disease recurrence after transurethral resection, as an alternative to BCG-naïve patients or to failed intravesical BCG therapy.
Methods: An extensive literature search on the use of siGD for BCG-naïve or BCG-refractory NMIBC was done using the following terms: non-muscle invasive bladder cancer, intravesical Gemcitabine and Docetaxel. Search results were filtered to include all retrospective studies and randomized controlled trials reporting the oncological outcomes of siGD published over the last 5 years from the conception of this study. Information on the safety profile and adverse events related to therapy were also reported, if available.
Results: The authors' search yielded 8 retrospective articles describing the efficacy of siGD for NMIBC, 5 of which had complete and accessible English manuscripts. A total of 476 low to high-risk NMIBC patients were included in the 5 eligible studies, 31 (6.5%) of which were BCG-naïve, while the rest failed BCG therapy. The reported one and two-year success rates were 54-69% and 34-55%, respectively. The recurrence-free survival rates at 1 and 2 years were 49-60% and 29-46%, respectively. Bladder cancer-specific mortality at 1 and 2-years were 1-3% and 4-11%, respectively. Treatment-related adverse reactions were mostly mild, the most common of which were urinary frequency, urgency, hematuria, and dysuria.
Conclusion: Sequential intravesical Gemcitabine and Docetaxel is a feasible alternative for BCG-naïve and BCG-refractory NMIBC patients. Oncological outcomes are comparable to BCG therapy with less adverse effects.

Key words: Intravesical chemotherapy, non-muscle invasive bladder cancer

Introduction

Bladder cancer is the 20th most common cancer and is the 21st leading cause of cancer-related deaths in the Philippines.[1] Ninety percent of bladder cancers are urothelial in histology and 75% of these cases would present as non-muscle invasive disease.[2-3] Performance of a high-quality transurethral resection of bladder tumor (TURBT) is the first step in managing bladder cancer as it offers histologic and staging information, therapeutic benefits, and disease prognostication.[4-6] The standard of care for high-risk non-muscle invasive urothelial bladder cancer after TURBT involves the administration of intravesical Bacillus Calmette-Guerin (BCG).[4-6] However, the recent

shortage in the production of the two major BCG strains worldwide has restricted their use for newly diagnosed NMIBC.[7] This translated to the limited availability of intravesical BCG in the Philippines since 2019. In addition to this supply issue, despite intravesical BCG therapy, bladder cancer recurrence is still recorded to be 40-50% in 5 years, with recurrence rates found to be as high as 78% in highest risk groups.[8-10] Non muscle invasive bladder cancer (NMIBC) patients who are unable to undergo intravesical BCG therapy (BCG-naïve) or those with disease progression after BCG therapy (BCG-refractory) are usually advised to undergo radical cystectomy. However, a lot of these patients may not readily agree to extirpative bladder excision either because they fear disfigurement issues related to an ileal conduit or they are unwilling to perform self-catheterization of an orthotopic neobladder. For these reasons, bladder conservation therapies should be considered.

Several intravesical agents have been studied as a substitute or adjunct to intravesical BCG. The most well-studied intravesical combinations for NMIBC include BCG + interferon, Quadruple immunotherapy (BCG + interferon+IL-2+GM-CSF), Gemcitabine + Mitomycin C, and Gemcitabine + Docetaxel. However, among these contemporary combination intravesical therapies, the combination of Gemcitabine and Docetaxel can be more widely used by clinicians due to its modest safety profile in comparison to the other combination therapies.[11] These two chemotherapeutic agents are also readily available in the Philippine setting.

This study aimed to determine the efficacy of sequential intravesical Gemcitabine and Docetaxel (siGD) among BCG-naïve, BCG-refractory or BCG-intolerant NMIBC patients in preventing disease recurrence or progression through a literature review.

Methods

Literature search was done in PubMed, Science Direct, Journal of Urology, European Journal of Urology and Journal of Clinical Oncology for journals pertaining to the use of sequential intravesical Gemcitabine and Docetaxel for BCG-naïve and/or BCG-refractory NMIBC using the following search terms: non-muscle invasive bladder cancer, and intravesical Gemcitabine and Docetaxel. The search results were filtered to include retrospective studies and randomized controlled trials reporting the oncologic outcomes of sequential intravesical Gemcitabine and Docetaxel therapy published in the last 5 years from the conception of this study. Only journals with available, complete English manuscripts were included for review. Separate data collection (i.e. population demographics, treatment protocol, and oncologic outcomes) from eligible journals were done by the two authors and any disparity from derived information were reconciled prior to reporting (Figure 1). Information on the safety profile and treatment-related adverse events were also reported, if available.

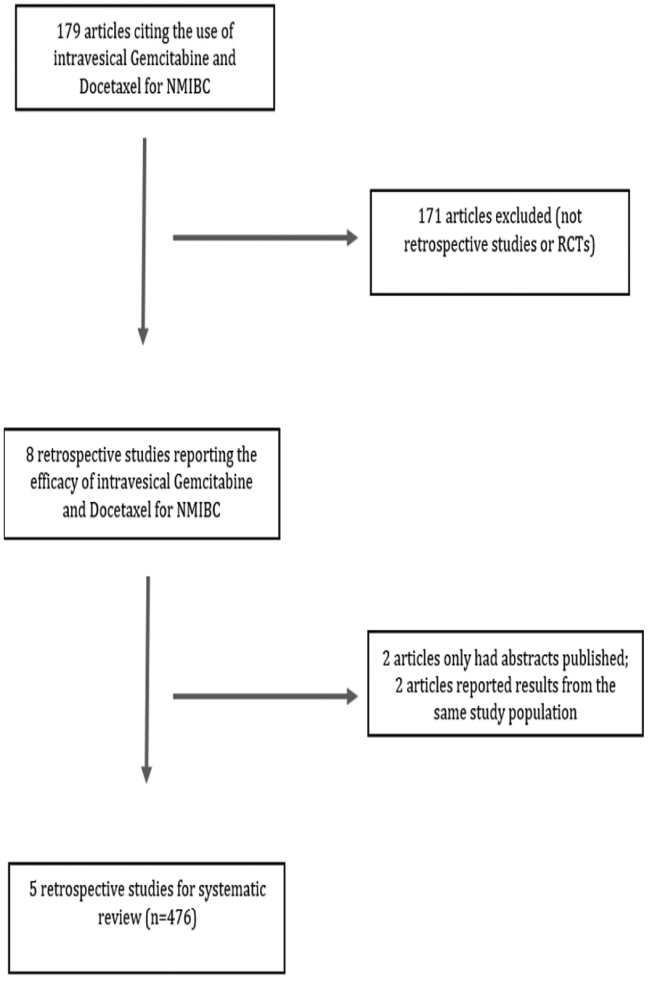

Figure 1. Flow chart of literature search

Results

Using the search terms and taking into account duplications in search results, a total of 179 articles were independently reviewed by the 2 authors. After applying the inclusion criteria, 8 articles reporting the oncologic outcomes of sequential intravesical Gemcitabine and Docetaxel for NMIBC were obtained. Two studies only had published abstracts, thus, were excluded from review. On further review, two journals reported the outcomes from the same study population, hence, the results of which were reported as one information derived from eligible journals.

The earliest reported outcomes of siGD were published by Steinberg, et al. from the University of Iowa in 2015.[12] They retrospectively analyzed 45 patients 4 (8.89%) BCG-naïve and 41 (91.11%) with previous intravesical BCG treatment with intermediate or high risk NMIBC who were given 6-weekly induction courses of intravesical Gemcitabine 1 g in 50 cc sterile water for 90 minutes followed by Docetaxel 37.5 in 50 mL normal saline for 120 minutes. Of those who received previous intravesical BCG, 19 were BCG refractory, 18 were BCG relapsing, and 4 were BCG intolerant. Five patients presented with symptoms (i.e. dysuria, frequency, urgency, hematuria, nausea) rendering them unable to complete induction intravesical chemotherapy. Of the 40 patients who completed induction treatment, success rate was reported to be 66% at first surveillance (12 to 16 weeks after treatment), 54% at 1 year, and 34% at 2 years. Median overall follow-up for treatment success was 5.9 months; 30 patients with initial treatment success had median follow-up of 12.5 months while those who failed treatment had median follow-up of 3.1 months. Of the 30 potential cystectomy candidates in this study, 10 (33.3%) underwent cystectomy at a median period of 5.6 months. With a median overall follow-up for survival determination at 15.4 months, all-cause mortality rate was 8% at 1 year and 20% at 2 years while bladder cancer-specific mortality rate was 3% and 11%, respectively.

In 2017, Milbar, et al. performed a retrospective analysis similar to the aforementioned study.[13] In their analysis of 33 low to high-risk NMIBC patients, 8 (24%) patients were BCG naïve, 3 (9%) were BCG intolerant, and 22 (66%) were BCG unresponsive/relapsing. They gave 6 weekly courses of 1g Gemcitabine in 50 cc sterile water left to dwell intravesically for 60 minutes followed by 37.5g Docetaxel in 50cc PNSS with a 60-minute dwell time. Seven out of the 33 (21%) patients had maintenance sequential intravesical Gemcitabine and Docetaxel given monthly after post-induction therapy surveillance. Two patients with CIS pathologies were unable to tolerate treatment while others only presented with mild symptoms, specifically: LUTS (9/33, 27%), increased frequency (7/33, 21%), increased urgency (6/33, 18%), exhaustion (4/33, 12%), pain (3/33, 9%), body flushing/erythema (2/33, 6%), limb cramps (2/33, 6%), incontinence (1/33, 3%), general flu-like symptoms (1/33, 3%), decreased appetite (1/33, 3%), and lightheadedness (1/33, 3%). Thirty six percent of patients did not experience any adverse reactions during treatment. Of the 8 BCG-naive patients, 3 (38%) recurred with high-grade disease while another 3 (39%) experienced low-grade recurrence. The BCG unresponsive/relapsing group had 25 patients, 22 (88%) of which presented with high-grade disease prior to therapy. Thirteen (52%) patients in the BCG unresponsive/relapsing group had high-grade recurrence after therapy while 2 (8%) experienced low-grade recurrence. Mean overall follow-up for the entire cohort was 17.6 months. Fifty percent (8/16) of high-grade events occurred during the initial 6 months of follow-up. One-year HG-RFS was 56% and 2-year DFS was 42%. Median DFS was 6.5 months with 23/33 (70%) patients demonstrating response at first surveillance. Of the patients who initially presented with high-grade disease, 1-year HG-RFS was 51% and 2-year HG-RFS was 34% with a median HG-RFS of 15.7 months. Median time to high grade recurrence was 6 months. Seven out of 15 (47%) of high-grade events among initially high-grade patients occurred in the initial 6 months of follow-up. BCG-naïve patients had a median DFS of 6.5 months with 50% 1-year DFS and 25% 2-year DFS while BCG unresponsive/relapsing patients had a median DFS of 6.5 months with a 1-year DFS of 38% and 2-year DFS of 24%. BCG-naïve patients had a 75% 1-year HG-RFS and 63% 2-year HG-RFS while BCG unresponsive/relapsing patients had a 49% 1-year HG-RFS and 34% 2-year

HG-RFS (median HG-RFS was 6.5 months). Of the patients who initially presented with low-grade disease, 1 had high-grade recurrence at 4.6 months while the other 4 only had low grade recurrence occurring at 1.9-10.4 months. They also found that patients who initially presented with low-grade disease were more likely to recur with low-grade pathology and were less likely to have CIS at therapy initiation. Ten patients (33%) eventually underwent cystectomy, 1 from the BCG-naïve group (occurring at 3.7 months after therapy) and 8 from the BCG unresponsive/relapsing group (median time to cystectomy of 16.1 months). All-cause and bladder cancer-specific mortality were 3% (1/33) at 1 year and 6% (2/33) at 2 years.

As a follow-up to the previous study, Daniels, et al. reported their evaluation of monthly maintenance combination intravesical Gemcitabine and Docetaxel in patients with NMIBC.[14] They retrospectively analyzed 59 low to high-risk NMIBC patients: 6 were naïve to intravesical therapy, 14 had received 1 prior intravesical therapy, and 39 previously received 2 or more intravesical induction therapies; 10 were BCG-naïve among these patients. All study participants received 6 weekly cycles of intravesical chemotherapy consisting of 1g Gemcitabine in 76.32 mL of PNSS left to dwell for 60 minutes followed by 40 mg Docetaxel in 54 mL PNSS again left to dwell for 60 minutes. Monthly maintenance intravesical therapy consisting of the same medications were given to patients who showed no pathology on cystoscopy 6 weeks after induction intravesical chemotherapy with follow-up cystoscopies done every 3 months. Forty one out of the 59 patients (70%) demonstrated no evidence of disease (NED) during first surveillance. Thirty-one patients were maintenance therapy eligible, however, 24 were managed with observation alone while 17 were given monthly maintenance therapy as planned. With an overall median follow-up of 24 months, 1-year DFS was 49% while 2-year DFS was 29%. Among the patients who initially presented with high-grade disease (n=52), 1-year HG-RFS was 53% while 2-year HG-RFS was 35%; 31/52 (71%) showed no evidence of high-grade disease at 3 months. Overall median time to treatment failure was 10.4 months with intravesical Gemcitabine and Docetaxel producing similar outcomes in both therapy-naïve patients and those who received intravesical therapy previously. For maintenance therapy eligible patients, median follow-up for the observation group was 36 months while that of the maintenance therapy group was 26 months. There was a statistically significant difference in 1-year DFS between the observation group and maintenance therapy group (42% vs 81%, p=0.04.) Even the 2-year DFS in this study was higher in favor of the maintenance therapy group (32% vs 59%) although, was not statistically significant (p=0.45). For the 49 patients who failed at least 1 previous intravesical therapy, 1-year DFS was 48% and 2-year DFS was 32%. Thirty-three (67%) of those who previously failed at least 1 intravesical therapy were eligible for maintenance Gemcitabine and Docetaxel therapy, the 1 and 2-year DFS of which comparing those who underwent observation versus those who were given maintenance therapy are as follows: 42% vs 81% and 34% and 59%, respectively. Kaplan-Meier analysis of the aforementioned findings showed that DFS was greater for patients who received maintenance therapy compared to those who were observed for all eligible patients (p=0.04) and for eligible patient who had previous BCG failure (p=0.05). Of the 15/56 (25.4%) patients in this study who eventually underwent cystectomy, 13 (87%) had received intravesical Gemcitabine and Docetaxel for high-grade disease with a median time to cystectomy of 13.2 months.

With the hope of increasing the efficacy of sequential intravesical Gemcitabine and Docetaxel, Rao, et al. retrospectively studied the benefit of administering the said intravesical therapy under hyperthermic conditions.[15] Sixty low to high-risk NMIBC patients were given 6-weekly intravesical instillations consisting 200 mg Gemcitabine in 10 mL warm sterile water (heated to 43–45°C) left to dwell for 60 minutes followed by 20 mg Docetaxel in 10 mL sterile water left to dwell for 120 minutes. Maintenance therapy was also given afterwards, consisting of 3 weekly- treatments of the combination therapy at 3, 6 and 9 months follow-up. Among their patient cohort, 9 were BCG-naïve while 51 had previously failed BCG intravesical therapy. Thirty-one patients (52%) experienced symptoms attributable to treatment with 10 of these patients having symptoms which impacted treatment with short 1-week delays.

Side effects reported were mild fatigue (20%), hematuria (20%), mild urinary frequency/urgency (13%), dysuria (10%), and nocturia (7%). Overall treatment success was 83% at first surveillance, 69% at 1 year, and 55% at 2 years after induction therapy with a median follow-up of 14.9 months. Treatment success for those who previously failed BCG therapy at first surveillance, 1 year, and 2 years were 88%, 74%, and 56%, respectively. On univariate cox regression analysis, the authors found out that patients who underwent one BCG maintenance instillations prior to sequential intravesical Gemcitabine and Docetaxel were less likely to recur after receiving Gem/Doce (p=0.048, HR 0.91). In contrast, prior BCG/IFN treatments increased recurrence (p=0.046, HR 8.64). Furthermore, patients who underwent more total Gem/Doce instillations were less likely to recur (p=0.015, HR 0.86). Fifty-five patients from the entire study population were potential cystectomy candidates but only 3/55 (5.4%) eventually underwent cystectomy at a median period of 10.2 months. All-cause and bladder cancer specific survival were both 97.9% at 1 year. At 2 years, all-cause and bladder cancer specific survival were 85.9% and 94.6%, respectively.

The largest retrospective study evaluating the efficacy of sequential intravesical Gemcitabine and Docetaxel for NMIBC was recently published by Steinberg, et al.[16] Their multi-institutional study consisted of 279 low to high-risk NMIBC who previously received intravesical BCG. These patients received 6-weekly intravesical instillations of 1 g Gemcitabine in 50 cc sterile water left to dwell for 60 to 90 minutes followed by 37.5 mg Docetaxel in 50 mL saline left to dwell for 60 to 120 minutes. Among the study participants, 112 (40.6%) reported symptoms during treatment with 26 (9.4%) having symptoms which impacted treatment schedule. Nine patients (3.3.%) were unable to tolerate full treatment. Treatment delay in 17 patients were due to dysuria, hematuria, frequency/urgency or urinary retention. Overall RFS was 60% in 1 year and 46% in 2 years with a median follow-up of 10.5 months. For patient who initially presented with recurrence, median time to recurrence after Gem/Doce was 6.8 months with 44.4% (60/135 patients) recurring within 6 months. For patients who initially presented with CIS, 1-year RFS was 60% while 2-year RFS was 43%. In comparison, patient who initially presented with papillary disease (Ta/T1, low or high grade) had a 1-year RFS of 62% and 2-year RFS of 51%. Overall, HG-RFS was 65% in 1 year and 52% in 2 years. In addition, BCG unresponsive cases with any CIS had a 2-year HG-RFS of 50% compared to those with papillary disease alone demonstrating a 2-year HG-RFS of 58%. They also elucidated that clinical stage, presence/absence of CIS, number of prior BCG failures, and BCG unresponsive status did not have a statistically significant effect on disease recurrence. Furthermore, the use of maintenance instillation among initial responders was significantly associates with no disease recurrence. Overall, 43/279 (15.4%) patients underwent cystectomy at a median of 11.3 months. Bladder cancer specific mortality was 1% at 1 year and 4% at 2 years while all-cause mortality rate were 3% and 13%, respectively.

Discussion

The recent worldwide BCG shortage had a negative impact on the treatment of non-muscle invasive bladder cancer. Furthermore, tolerability of patients to intravesical BCG is an important issue to take into consideration given the fact that the limited supply of BCG should be reserved for eligible patients who are anticipated to tolerate the full induction and maintenance course. This prompted the urologists to seek alternative intravesical therapies with comparable efficacy to BCG in terms of preventing disease recurrence and progression. Several intravesical chemotherapeutic and immunologic agents, usually used in combination, have been cited by several studies. As was stated earlier, the most well-studied and promising alternative combination intravesical therapy for NMIBC to date is sequential Gemcitabine and Docetaxel.

Gemcitabine is anti-cancer nucleoside which acts by preventing DNA elongation while Docetaxel is an inhibitor microtubule disassembly thereby inhibiting cell division.[17-18] The synergistic effect of this combination may be due to effect of Gemcitabine which acts as an exfoliant to urothelial cells in the urinary bladder. They may

then potentially increase the cellular penetrance of Docetaxel.[19] The sequential administration of the said chemotherapeutic agents have resulted to acceptable recurrence-free rates for NMIBC with a good safety profile in lieu of the BCG shortage as shown by our literature review.[12-16] It is also notable that chemohyperthermia may increase the efficacy of intravesical Gem/Doce as shown by the numerically higher success rates in the study done by Rao, et al. in comparison to the other studies.[15] This perceived benefit of hyperthermia may be due to the following mechanisms: 1) increased drug penetration into the urothelium due to increased cellular membrane permeability and/or modified blood perfusion; 2) direct cytotoxicity by altering intracellular metabolism causing DNA damage thereby impairing cellular division and increasing tumor cell apoptosis; and 3) increased drug cytotoxic effect.[20]

Based on available literature, siGD has very good safety profile and tolerability with side effects mostly consisting of mild to moderate LUTS, dysuria, or hematuria; the largest study in this review reported that only 9.4% of patients had symptoms severe enough to impact treatment. In addition, the risk of severe BCG toxicity and other systemic side effects associated with the use of immunotherapy are absent in siGD. With intravesical BCG therapy having a 5-year recurrence rate of 40%-50%, siGD has shown to have a relatively comparable impact on NMIBC recurrence with 2-year RFS reaching 46%. However, the shorter follow-up period of the studies reporting the impact of siGD on disease recurrence has placed its treatment durability inferior to that of intravesical BCG. Furthermore, randomized controlled studies with longer follow-up periods are warranted to establish whether siGD has an impact on disease progression. Taking these into consideration, it may still be reasonable to offer intravesical BCG as first line adjuvant treatment for NMIBC. Sequential treatment with intravesical Gemcitabine and Docetaxel may be reserved for intermediate and high-risk NMIBC, when BCG becomes unavailable, or in patients who fear the risk of BCG toxicity.

Conclusion

The recent worldwide shortage in intravesical BCG has led to a constant search for alternative agents with equivalent efficacy. This systematic review has shown that sequential intravesical Gemcitabine and Docetaxel is a feasible alternative with comparable short-term efficacy and superior safety profile for NMIBC patients. Further studies are needed to determine long-term oncologic outcomes of the said drug combination. In addition, randomized control trials comparing Gem/Doce to BCG may be warranted in the future to confirm the former's non-inferiority to the latter.

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Summary of Systematic Review

Study Author, Year Published	Population Size (n) and Characteristics	Description of Treatment Protocol	Oncologic Outcomes	Adverse Effect
Steinberg et. al., 2015	45 intermediate to high risk NMIBC patients: 4 BCG-naïve, 41 with previous intravesical BCG treatment	6 -weekly intravesical instillations: 1g Gemcitabine 50 cc sterile water for 90 minutes + 37.5g Docetaxel in 50 mL NSS for 120 minutes	- Overall treatment success: 66% at 12-16 weeks after treatment, 54% at 1 year, 34% at 2 years - All-cause mortality: 8% at 1 year, 20% at 2 years - Bladder cancer-specific mortality: 3% at 1 year, 11% at 2 years	5 patients unable to complete treatment due to symptoms (dysuria, frequency/urgency, hematuria, nausea)

Milbar et. al., 2017	33 low to high risk NMIBC patients: 8 BCG-naïve, 3 BCG intolerant, and 22 BCG unresponsive/relapsing	- 6-weekly intravesical instillations: 1g Gemcitabine in 50 cc sterile water for 60 minutes + 37.5 mg Docetaxel in 50 cc PNSS for 60 minutes (7 patients received monthly maintenance treatment)	- BCG-naïve: 38% high-grade recurrence, 39% low-grade recurrence - BCG unresponsive/ relapsing: 52% high-grade recurrence, 8% low-grade recurrence - 1-year HG-RFS: 56% - 2-year DFS: 42% - Median DFS: 6.5 months - For high-grade disease: 1-year HG-RFS 51%, 2-year HG-RFS 34%; Median HG-RFS 15.7 months - For BCG-naive: 1-year DFS 50%, 2-year DFS 25%, median DFS 6.5 months; 1-year HG-RFS 75%, 2-year HG-RFS 63% - For BCG unresponsive/relapsing: 1-year DFS 50%, 2-year DFS 25%, median DFS 6.5 months; 1-year HG-RFS 49%, 2-year HG-RFS 34% - 9 patients underwent cystectomy: 1 BCG-naive, 8 unresponsive/relapsing (median time to cystectomy 16.1 months) - All-cause and bladder cancer specific mortality: 3% at 1 year, 6% at 2 years	2 patients with CIS were unable to tolerate treatment - LUTS (27%), frequency (21%), urgency (18%), exhaustion (12%), pain (9%), body flushing/erythema (6%), limb cramps (6%), incontinence (3%), decreased appetite (3%), lightheadedness (3%)
Daniels et. al., 2020	59 low to high-risk NMIBC patients: 6 intravesical therapy-naïve, 14 received 1 prior intravesical therapy, 39 received 2 or more prior intravesical therapy; 10 BCG-naïve	- 6-weekly intravesical instillations: 1g Gemcitabine in 76.32mL PNSS for 60 minutes + 40 mg Docetaxel in 54 mL PNSS for 60 minutes - Monthly maintenance given to patients who showed no pathology on 6 weeks post-induction surveillance	- 70% no evidence of disease on first surveillance - 1-year DFS: 49% - 2-year DFS: 29% - For high-grade disease (n=52): 1-year HG-RFS 53%, 2-year HG-RFS 35% - Overall median time to treatment failure: 10.4 months	Not reported

Rao et. al., 2020	60 low to high-risk NMIBC patients (9 BCG-naïve, 51 previously failed BCG therapy)	- 6-weekly intravesical instillations of 200 mg Gemcitabine in sterile water left to dwell for 60 minutes followed by 20 mg Docetaxel in 10 mL sterile water left to dwell for 120 minutes (diluents heated to 43-45 °C) + 3 weekly-treatments maintenance therapy at 3-month intervals	- Overall treatment success: 83% at first surveillance, 69% at 1 year, and 55% at 2 years - Treatment success for those with previous BCG: 88% at first surveillance, 74% at 1 year, 56% at 2 years - 2-year all-cause survival: 85.9% - 2-year bladder cancer specific survival: 94.6%	52% presented with symptoms: mild fatigue (20%), hematuria (20%), mild urinary frequency/urgency (13%), dysuria (10%), and nocturia (7%)
Steinberg et. al., 2020	279 low to high-risk NMIBC patients who previously received intravesical BCG	6-weekly instillations of 1g Gemcitabine in 50 cc sterile water left to dwell for 60 to 90 minutes followed by 37.5 mg Docetaxel in 50 mL saline left to dwell for 60 to 120 minutes	- Overall RFS: 60% in 1 year, 46% in 2 years - Median time to recurrence for those who initially presented with recurrence: 6.8 months - For CIS: 60% 1-year RFS, 43% 2-year RFS - For Ta/T1, low or high grade: 62% 1-year RFS, 51% 2-year RFS - Overall HG-RFS: 65% in 1 year, 52% in 2 years - Bladder cancer specific mortality: 1% at 1 year, 4% at 2 years - All-cause mortality: 3% in 1 year, 13% at 2 years	- 112 (40.6%) reported symptoms during treatment with 26 (9.4%) having symptoms which impacted treatment schedule - Treatment delay in 17 patients were due to dysuria, hematuria, frequency/urgency or urinary retention

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