

Retrospective analysis of the efficacy and safety of neoadjuvant gemcitabine and cisplatin in muscle-invasive bladder cancer

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Abstract

Background: Neoadjuvant cisplatin-based combination chemotherapy for muscle-invasive bladder cancer (MIBC) improves overall and disease-free survival. However, there is much debate over the optimal neoadjuvant regimen. Gemcitabine plus cisplatin (GC) has been the neoadjuvant regimen of choice for many institutions for patients with MIBC based on data extrapolated from the metastatic setting. Based on recent data, many institutions are transitioning to variations of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) as the neoadjuvant regimen of choice.

Objective: To assess the effectiveness and safety of neoadjuvant chemotherapy with gemcitabine plus cisplatin in patients with muscle-invasive bladder cancer prior to cystectomy.

Methods: This is a single-center, retrospective, cohort study at Duke University Hospital (DUH). Patients included had MIBC and received gemcitabine plus cisplatin chemotherapy prior to a cystectomy. The primary endpoint was to assess the pathologic complete response (pCR) rate in MIBC after treatment with gemcitabine and cisplatin. Patients were split into two groups, those who received their chemotherapy at DUH, and those who received their chemotherapy at an outside facility.

Results: Overall pCR rate for all patients ($n = 36$) was 14%. The pCR rates for patients in the Duke Chemotherapy Group ($n = 17$) and in the Community Chemotherapy Group ($n = 19$) were 24% and 5%, respectively. GC was overall well tolerated in most patients with few adverse events \geq grade 3.

Conclusions: This retrospective study demonstrates a consistent pCR rate (24% in Duke Chemotherapy Group) for neoadjuvant GC in MIBC compared with other literature. The overall pCR rate for all patients was 14%.

Keywords

Urinary bladder neoplasms, gemcitabine, cisplatin, neoadjuvant therapy

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Introduction

Bladder cancer is the fourth most common cancer diagnosed among men in the United States. In 2018, it is estimated that 81,190 new cases of bladder cancer will be diagnosed and there will be approximately 17,240 deaths due to bladder cancer.¹ For patients with localized muscle-invasive bladder cancer (MIBC), standard management is considered to be a radical cystectomy. However, approximately 30% of patients will have disease recurrence if treated with surgery alone.² Neoadjuvant chemotherapy is thus commonly used to reduce recurrence rates and improve survival by attempting to eradicate micro-metastatic disease.

Neoadjuvant cisplatin-based combination chemotherapy for patients with MIBC was shown to prolong overall survival compared to surgery alone in two large

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randomized trials and in two meta-analyses.³⁻⁶ Combination neoadjuvant chemotherapy demonstrated a 33% reduction in the risk of death compared to the cystectomy alone group.³ The advantage of platinum-based combination neoadjuvant chemotherapy was further confirmed by an absolute five-year overall survival benefit of 5% (HR: 0.86; 95% CI: 0.77-0.95) and improved absolute disease-free survival at five years of 9% (HR: 0.78; 95% CI: 0.71-0.86).⁷ Despite such level 1 evidence, neoadjuvant chemotherapy continues to be underutilized. An analysis of the National Cancer Data Base showed that the use of neoadjuvant chemotherapy increased from 10.1% in 2006 to 20.8% in 2010.⁸

The most effective neoadjuvant regimen based on clinical trials is MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin). The Southwest Oncology Group (SWOG)-8710 randomized trial of 317 patients with muscle-invasive bladder cancer demonstrated a significant improvement in median survival in patients treated with MVAC compared to cystectomy alone (77 vs. 46 months, $P=0.05$) and a trend towards improvement in five-year overall survival.³ However, many oncologists use gemcitabine plus cisplatin (GC) as the neoadjuvant chemotherapy treatment of choice. A survey of medical oncologists within the Bladder Cancer Advocacy Network or American Society of Clinical Oncology showed that, among various chemotherapy regimens, GC was the most commonly used reported by 89% of the respondents, whereas 29% reported using MVAC and 19% reported using dose-dense MVAC.⁹ In this survey, respondents could report using more than one regimen. GC was compared to MVAC in a randomized trial of patients with metastatic bladder cancer and, while this was a superiority trial designed to detect a difference in efficacy and not test for similar efficacy, GC appeared to have similar efficacy, including overall survival, with less toxicity.¹⁰ These data are often extrapolated for use in the neoadjuvant setting, even though GC was never formally evaluated in a prospective trial of MIBC.

There remains much debate on the optimal neoadjuvant chemotherapy regimen. At the time of this study, with recently published phase II data on accelerated or dose-dense MVAC neoadjuvant therapy, our institution started to use the accelerated MVAC regimen for qualifying patients over the previously favored GC regimen for neoadjuvant therapy.^{11,12} However, the Duke experience with neoadjuvant gemcitabine plus cisplatin has never been evaluated. The primary objective of this study was to describe the clinical efficacy of GC in the neoadjuvant setting for MIBC at Duke University Hospital (DUH). Pathologic complete response was chosen as the primary endpoint as it has been shown that following cystectomy, 85% of patients who achieved a pCR were alive at five years.³

Secondary objectives were to describe disease recurrence, time to surgery, chemotherapy dosing, adverse effects, perioperative complications, and tumor downstaging/upstaging.

Materials and methods

Patient population

In this single-center, retrospective study, patients were included who had measurable and histologically proven, predominately urothelial, muscle-invasive bladder cancer (cT2-T4, N any, M0) and received a cystectomy at Duke University Hospital between 1 January 2008 and 31 December 2013 and were treated with neoadjuvant gemcitabine plus cisplatin chemotherapy. Patients were excluded if they were treated with other chemotherapy agents after diagnosis and prior to gemcitabine plus cisplatin (after cisplatin was initiated, substitution of carboplatin in place of cisplatin was allowed as necessary), if they received prior chemotherapy for other cancer diagnoses within the previous 12 months, or if they had received their chemotherapy at an outside institution and had an incomplete chemotherapy treatment history in the medical record. This study was approved by the institutional review board (IRB) at Duke University Hospital.

Retrospective data collection

Following IRB approval, patients were identified through a query of the Duke Enterprise Data Unified Content Explorer (DEDUCE) and the electronic medical record system. The DEDUCE query included patients with a diagnosis of bladder cancer who had received a radical or partial cystectomy by ICD 9 codes at Duke University Hospital between 1 January 2008 and 31 December 2013. The query of the electronic medical record system included patients treated with gemcitabine and/or cisplatin and seen by one of the medical oncology providers from 1 June 2013 to 31 December 2013 to capture patients in the new electronic medical record. The medical records of the identified patients based on the queries were then reviewed for inclusion and exclusion criteria. The patients who were included were subsequently divided into two groups: The Duke Chemotherapy Group (DCG) and The Community Chemotherapy Group (CCG). The DCG included patients who received both chemotherapy and a cystectomy at Duke University Hospital. Complete information for all primary and secondary outcomes was collected in this group. The CCG included patients who were initially evaluated at Duke by a medical oncologist but then received their chemotherapy at a local treatment facility closer to

their home prior to undergoing a cystectomy at Duke. Information collected in this group included baseline characteristics, tumor upstaging and downstaging, length of stay (LOS) in the hospital following cystectomy, readmissions to the hospital following cystectomy, one-year disease recurrence and overall survival status. Other outcomes and specific drug doses were not available in the medical records of the CCG.

Clinical practice at Duke by the medical oncologists was to typically recommend gemcitabine and cisplatin (GC) chemotherapy for four cycles repeating every 21 days, with gemcitabine 1000 mg/m² given on days 1 and 8 and cisplatin 70 mg/m² given on day 1 of each cycle. Substitution of carboplatin in place of cisplatin was allowed, as this is occasionally necessary for patients who developed renal dysfunction. Doses and schedules were adjusted for chemotherapy during the course of treatment as deemed appropriate by the medical oncologist.

The primary endpoint of the study was pathologic complete response rate (downstaging to pT0) after neoadjuvant chemotherapy with GC at the time of cystectomy. The clinical stage at diagnosis after the transurethral resection of the bladder tumor (TURBT) and the pathologic stage at the time of cystectomy were collected. Secondary endpoints included tumor downstaging, tumor upstaging, disease recurrence, time to surgery, chemotherapy dosing intensity, adverse effects, and perioperative complications.

Tumor downstaging was defined as the achievement of non-muscle invasive disease (<pT2) at the time of cystectomy whereas tumor upstaging was defined as those with more invasive disease (i.e., higher T stage) at the time of cystectomy compared with initial clinical staging. Of note, tumor upstaging can be difficult to define precisely as the tumor can be classified as T2 + preoperatively because it is known to at least be T2, but often is T3. Disease recurrence was defined as the time from cystectomy to reappearance of local or regional disease, metastases, or death in the specified follow-up time period of one year. Data for disease recurrence were collected from the electronic medical record by finding the closest visit to one year from the start of chemotherapy \pm 30 days. Overall survival was assessed based on updated patient data available in the medical record at the conclusion of the study.

Time to surgery was reported in days from the start of neoadjuvant chemotherapy to cystectomy, as well as days from the last day of chemotherapy to surgery. Adverse effects that were collected during chemotherapy include renal dysfunction, hepatic dysfunction, myelosuppression, nausea/vomiting, neuropathy, and thromboembolic events. Acute kidney injury, anemia, thrombocytopenia, and leukopenia were defined as Grade 1-5 according to the Common Terminology Criteria for Adverse events (CTCAE) criteria Version 4.0 from the National Cancer

Institute. Hepatic failure was reported as Grade 3-5 according to the CTCAE criteria. Nausea and vomiting (N/V) were collected by assessing progress notes for documentation of severe nausea and vomiting unrelieved by pretreatment and medications prescribed after chemotherapy. Neuropathy and thromboembolic events (venous or arterial) were assessed through progress notes for documentation of these events during chemotherapy.

The perioperative complications that were assessed include the length of hospital stay and readmission rate. The length of hospital stay was calculated according to the number of days the patient remained hospitalized following cystectomy. Readmission rates were calculated as any readmission to the hospital within 45 days of the cystectomy.

Statistical analysis

Descriptive statistics were utilized to evaluate all endpoints including pathologic complete response rate (primary outcome), tumor downstaging/upstaging, disease recurrence, time to surgery, chemotherapy dose intensity, perioperative complications, and adverse events (secondary outcomes). The descriptive statistics for continuous variables are reported as mean and median (range). Categorical variables report counts and percentages.

Results

Based on the initial queries of the DEDUCE and electronic medical record systems, 266 patients were identified, of which 230 were excluded (Figure 1). Thirty-six patients met the inclusion criteria and were thus included

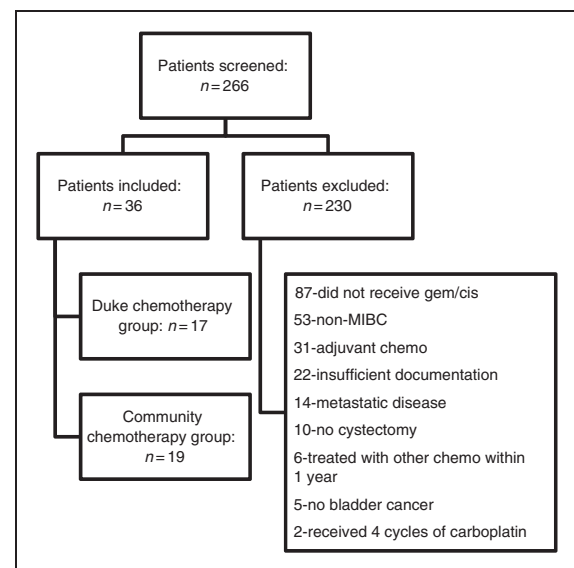


Figure 1. Study cohort selection process.

in the analysis. Common reasons for exclusion include that the patients did not receive gemcitabine or cisplatin ($n = 86$), either not at all or that they did not receive the combination, or that they did not have muscle-invasive bladder cancer ($n = 53$). Thirty-one patients were excluded because they received adjuvant chemotherapy. Patients were excluded based on the first finding of an exclusion criterion in the medical record. Of the 36 included patients, 17 were included in the DCG and 19 were included in the CCG. Overall, the mean age was 62 years, 64% were male, and 89% were Caucasian. Baseline characteristics are listed in Table 1.

None of the patients included received more than four cycles of gemcitabine and cisplatin. Of those in the DCG, one patient received two cycles of chemotherapy at Duke and two cycles at a local treatment facility, and three patients received three out of four cycles of chemotherapy overall. One patient did not complete the fourth cycle due to severe nausea and vomiting and other side effects, another due to side effects of neuropathy and the development of a hepatic abscess during chemotherapy, and the third patient only received three cycles due to increasing serum creatinine prior to cycle four of chemotherapy. One patient in the CCG received one cycle of cisplatin and the remaining three cycles of carboplatin. Additionally, in terms of dose intensity, all of the DCG patients received full dose gemcitabine and cisplatin with the exception of three patients.

One patient received dose-reduced cisplatin for cycle one followed by full dose, one patient received dose-reduced cisplatin for two cycles, and the third patient received dose-reduced cisplatin and gemcitabine for cycles 2–4 after being hospitalized for febrile neutropenia after cycle one. Of note, no dose intensity data for the CCG patients could be obtained.

Overall, the pathologic complete response rate to pT0 for both groups was 14% ($n = 5$). Twenty-four percent ($n = 4$) of patients in the DCG achieved a pT0 stage, while 5% ($n = 1$) in the CCG achieved a pT0 stage (Table 2). Overall tumor downstaging to non-muscle invasive disease or pT0 was 36% ($n = 13$)—47% in the DCG ($n = 8$) and 26% in the CCG ($n = 5$). Tumor upstaging from prior to chemotherapy at cystectomy was 28% ($n = 10$) overall, which was similar between the groups. Thirteen patients (36%) overall had no change in their staging following chemotherapy at the time of cystectomy—24% ($n = 4$) in the DCG and 48% ($n = 9$) in the CCG (Table 2).

Regarding the secondary endpoints, the median time to surgery from day one of chemotherapy was 118 days and the median time to surgery from the end of chemotherapy was 50 days. This endpoint was only evaluated in the DCG where complete data on dates and doses of chemotherapy were available in the electronic medical record. The median length of stay (LOS) in the hospital following cystectomy was nine days overall between

Table 1. Baseline characteristics.

| | All patients ($n = 36$) | Duke chemotherapy ($n = 17$) | Community chemotherapy ($n = 19$) |
|--------------------------|---------------------------|--------------------------------|-------------------------------------|
| Age at diagnosis (years) | | | |
| Mean (SD) | 62.3 (8.70) | 61.4 (7.76) | 63.1 (9.59) |
| Median (Q1–Q3) | 63.4 (57.8–67.5) | 62.3 (57.8–66.3) | 64.3 (57.6–67.9) |
| (Min, Max) | (38.2, 80.2) | (47.0, 74.7) | (38.2, 80.2) |
| Gender—no. (%) | | | |
| Male | 23 (64) | 9 (53) | 14 (75) |
| Female | 13 (36) | 8 (47) | 5 (25) |
| Race—no. (%) | | | |
| Caucasian | 32 (89) | 16 (94) | 16 (84) |
| BMI | | | |
| Mean (SD) | 27.2 (6.30) | 27.5 (6.28) | 26.9 (6.47) |
| Clinical T stage—no. (%) | | | |
| cT2 | 26 (72) | 13 (76) | 13 (68) |
| cT3 | 7 (20) | 4 (24) | 3 (16) |
| cT4 | 3 (8) | 0 (0) | 3 (16) |
| N stage—no. (%) | | | |
| NX | 26 (72) | 13 (76) | 13 (68) |
| N0 | 10 (28) | 4 (24) | 6 (32) |
| M stage—no. (%) | | | |
| M0 | 36 (100) | 17 (100) | 19 (100) |

Table 2. Tumor upstaging and downstaging.

| | All patients (n = 36) | Duke chemotherapy (n = 17) | Community chemotherapy (n = 19) |
|---|-----------------------|----------------------------|---------------------------------|
| Pathologic complete response rate—no. (%) | 5 (14) | 4 (24) | 1 (5) |
| Overall tumor downstaging—no. (%) | 13 (36) | 8 (47) | 5 (26) |
| Tumor upstaging—no. (%) | 10 (28) | 5 (29) | 5 (26) |
| cT2 to pT3 | 6 (17) | 3 (18) | 3 (16) |
| cT2 to pT4 | 4 (11) | 2 (11) | 2 (10) |
| No change—no. (%) | 13 (36) | 4 (24) | 9 (48) |

Table 3. Disease recurrence and survival.

| | All patients (n = 36) | Duke chemotherapy (n = 17) | Community chemotherapy (n = 19) |
|--|-----------------------|----------------------------|---------------------------------|
| 1 Year follow-up—no. (%) | | | |
| No disease recurrence | 20 (55) | 12 (71) | 8 (42) |
| Disease recurrence | 11 (31) | 5 (29) | 6 (32) |
| Unknown | 5 (14) | 0 (0) | 5 ^a (26) |
| Survival status—no. (%) | | | |
| Alive with disease | 4 (11) | 3 (18) | 1 (5) |
| Alive with no evidence of disease | 11 (31) | 5 (29) | 6 (32) |
| Dead | 14 (39) | 8 (47) | 6 (32) |
| Unknown | 5 (14) | 1 (6) | 4 (21) |
| Alive with disease status unknown | 2 (5) | 0 (0) | 2 (10) |
| Average time from diagnosis to date of last contact or death—days, years | – | 912 days, 2.5 years | 822 days, 2.25 years |

^aThe status of these five patients in the CCG are unknown as they were lost to follow-up.

both groups. Median LOS in the DCG was eight days (range: 4–21) and 10 days (range: 6–43) in the CCG. Readmissions to the hospital within 45 days following cystectomy was 31% overall –29% (n = 5) in the DCG and 32% (n = 6) in the CCG.

At one year after cystectomy (± 30 days), 55% of patients overall had not had disease recurrence, while 31% of patients had disease recurrence. Differences between the DCG and CCG exist because five patients in the CCG were lost to follow-up and their disease status could not be determined (Table 3). Among the 14 CCG patients with known disease status one year after cystectomy, 57% had no disease recurrence and 43% had disease recurrence. At the one-year analysis cutoff, 31% of patients were alive with no evidence of disease, 39% of patients were deceased, and 11% of patients were alive with disease.

Adverse effects

In the DCG, adverse events were reported using the CTCAE criteria. There were no cases of acute kidney

injury or hepatic failure due to chemotherapy. There were four cases of Grade 3 anemia with each of the patients requiring transfusion with packed red blood cells. One patient was hospitalized due to anemia. There was one case of grade 2 thrombocytopenia and two cases of grade 3 thrombocytopenia. One patient experienced grade 3 leukopenia requiring hospitalization. Of the 17 patients in the DCG, 41% (n = 7) experienced severe nausea and vomiting requiring additional provider and pharmacologic intervention, 18% (n = 3) suffered from neuropathy, and 12% (n = 2) experienced a thromboembolic event during treatment.

Discussion

This retrospective analysis of gemcitabine and cisplatin in patients with muscle-invasive bladder cancer showed an overall pathologic complete response rate to pT0 of 14% and an overall tumor downstaging rate to stage <pT2 of 36%. Although the overall pathologic complete response rate was less than expected, the pathologic complete response rate in the DCG of

24% was as expected based on previously published data. The aim of this project was to evaluate our previous practice with GC neoadjuvant chemotherapy as many patients have begun to receive accelerated MVAC neoadjuvant chemotherapy at our institution.

The benefit of neoadjuvant GC has yet to be validated in a prospective randomized study. Therefore, current clinical practice is reliant upon retrospective analyses to quantify the pathologic efficacy and toxicity of GC in this setting. A retrospective study from the University of Calgary showed a 21% downstaging rate to pT0 in 91 patients with MIBC who received neoadjuvant GC and a downstaging rate to <pT2 of 37%.¹³ Scosyrev et al. at Strong Memorial Hospital conducted a retrospective analysis from 1999 to 2009 with GC neoadjuvant chemotherapy and showed a tumor downstaging rate to pT0 at cystectomy of 20% and a tumor downstaging rate to <pT2 of 44%.¹⁴ In our analysis, the pathologic complete response rate to pT0 in the DCG of 24% is consistent with these other retrospective studies. The pathologic complete response rate in the CCG, however, was lower at only 5%, bringing the overall pT0 rate to only 14%. The small patient numbers in our study preclude any statistical comparison between the two groups. Determining a cause for this numerical difference between the two groups is difficult given the retrospective nature of the study and the lack of complete chemotherapy dosing and schedule history for patients in the CCG. The relative dose intensity between the groups is also unknown and could contribute to differences in outcomes. One prior retrospective analysis similarly included patients who had received their chemotherapy at an outside institution, but the downstaging rate was reported as an overall number and not subdivided as in our study.¹⁵ Also similar to these previous studies, the tumor downstaging rate to <pT2 in our analysis was 36%.

With comparable response rates between our analysis and prior studies with GC neoadjuvant chemotherapy, we next sought to extrapolate our results to other retrospective analyses comparing GC with MVAC. Further retrospective studies have compared neoadjuvant GC with MVAC showing similar pathologic outcomes between the two regimens. Yeshchina et al. at Columbia University retrospectively compared perioperative GC with MVAC in 114 patients, of which 61 received neoadjuvant chemotherapy (16 with GC and 45 with MVAC). Of these patients, 31% of the MVAC patients and 25% of the GC patients achieved a pathologic complete response at either cystectomy or during cystoscopy for those refusing radical surgery ($p=0.645$). They also showed similar rates of downstaging to non-muscle invasive disease—44% in the MVAC group and 50% in the GC group ($p=0.702$). Importantly, the choice of regimen also had no impact

on disease-related death ($p=0.492$).¹⁶ Another retrospective analysis by Pal et al. at the City of Hope Cancer Center reviewed neoadjuvant chemotherapy in 61 patients, of which 24 were treated with GC, 22 with MVAC, and 15 with an alternative regimen. Pathologic response to <pT2 disease was seen in 41.7% of GC patients and 50% of MVAC patients with no statistical difference seen in overall survival between the two groups ($p=0.73$).¹⁵ Lee et al. also retrospectively compared neoadjuvant GC and MVAC in 72 identified patients, showing similar pathologic complete response rates (pT0) of 29% and 22% as well as similar pathologic responses to <pT2 of 49% and 35% in the GC and MVAC patients, respectively.¹⁷ Likewise, Dash et al. at Memorial Sloan-Kettering Cancer Center found similar rates of pathologic complete response to pT0 and pathologic response to <pT2 in the 42 patients who received GC (26% and 36%, respectively) and the 54 patients who received MVAC (28% and 35%, respectively).¹⁸ Most recently, Galasky et al. reviewed 146 patients who received GC and 66 who received MVAC showing similar pathologic response to <pT1 (31% in GC patients versus 29% in MVAC patients).¹⁹ Based on the results of these retrospective studies, the neoadjuvant GC and MVAC regimens appear to be similarly effective. The pCR rates for the GC groups in these retrospective studies appear higher than the pCR rates seen in our overall patient population (14%) but similar when considering only the DCG patients (24%).

However, the treatment landscape for MIBC is changing. Two more recently published phase II studies of neoadjuvant dose-dense or accelerated MVAC have again caused institutions, including our own, to question which regimen should be the preferred neoadjuvant strategy. Choueiri et al. investigated neoadjuvant dose-dense MVAC (ddMVAC) with pegfilgrastim support in 39 patients with muscle-invasive bladder cancer (cT2-cT4, N0-1, M0).¹¹ After a planned four cycles of chemotherapy, the rates of pathologic complete response (pT0) and pathologic response to <pT2 were 26% and 49%, respectively. In addition, at the time of cystectomy, 14 of the 17 patients with cN1 disease (82%) were pN0 on imaging. Importantly, 95% of the patients completed all four cycles of chemotherapy with only 10% experiencing high-grade (grade ≥ 3) chemotherapy-related toxicities, and no febrile neutropenia or treatment-related deaths were reported. Plimack et al. investigated a similar accelerated MVAC (AMVAC) neoadjuvant chemotherapy regimen with pegfilgrastim support in 40 patients with muscle-invasive bladder cancer (T2-T4a, N0-1, M0).¹² After a planned three cycles of chemotherapy, 38% of the patients had a pathologic complete response to pT0 while 53% overall were downstaged to non-muscle

invasive disease (<pT2). As with the ddMVAC, this regimen was also well tolerated as 93% of patients completed all three cycles of chemotherapy and only 12% reported grade 3 or 4 treatment-related adverse effects. The pathologic complete response rate of 26% reported by Choueiri was similar to rates with MVAC and GC in the previously discussed retrospective studies; however, the rate seen by Plimack et al.¹² was numerically greater than the majority of pathologic complete response rates with GC. Based on these data with dose-dense/accelerated MVAC, in addition to high rates of overall downstaging to non-muscle invasive disease, reduced time from chemotherapy initiation to cystectomy, and an overall favorable toxicity profile, we now consider accelerated MVAC as our preferred neoadjuvant treatment regimen for muscle-invasive disease.

Our study has several limitations. First, this was a retrospective, single-center, chart review and is thus subject to all of the potential biases associated with retrospective approaches. With only a total of 36 patients, the sample size was also small. In addition, over half of the patients received their chemotherapy at an outside facility, and data on the chemotherapy dosing and schedule for these patients are lacking. This study was not originally designed to compare the two groups, but to describe the overall population of muscle-invasive bladder cancer patients treated with neoadjuvant GC prior to a cystectomy at Duke University Hospital. As such, an adequate causal analysis for the differences between the two groups could not be performed. It is also important to note that there are several ongoing clinical trials investigating the use of immune checkpoint inhibitors, including the PD-L1 inhibitors atezolizumab, durvalumab, and avelumab and the PD-1 inhibitors nivolumab and pembrolizumab, in the neoadjuvant MIBC setting.^{20–24} The results of these ongoing trials could potentially impact the neoadjuvant treatment recommendations in MIBC.

In conclusion, this retrospective study at Duke suggests a consistent pathologic complete response rate for neoadjuvant GC in MIBC compared with other literature when considering the DCG. However, the overall pCR rate appears slightly lower. GC was overall well tolerated in most patients with few adverse events \geq grade 3 according to CTCAE criteria. Most patients treated at Duke finished the full four planned cycles of GC with few interruptions or delays in chemotherapy. Despite similar response rates noted between GC and MVAC in previous studies, our response rate with GC appears to be on the lower end of the expected range. As such and based on the results by Choueiri et al.¹¹ and Plimack et al.¹² discussed earlier, the Duke Genitourinary Medical Oncology group will continue to use accelerated MVAC as the preferred neoadjuvant

chemotherapy for selected patients. After further experience with the accelerated MVAC neoadjuvant chemotherapy regimen at our institution, we plan to compare the data from the current study with similar data from our MVAC patients in an attempt to determine the optimal regimen for patients with muscle-invasive bladder cancer at our institution.

Declaration of Conflicting Interests

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