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Gemcitabine and cisplatin neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma: Predicting response and assessing outcomes

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Abstract

Purpose—To evaluate gemcitabine-cisplatin (GC) neoadjuvant cisplatin-based chemotherapy (NAC) for pathologic response (pR) and cancer-specific outcomes following radical cystectomy (RC) for muscle-invasive bladder cancer and identify clinical parameters associated with pR.

Materials and methods—We studied 150 consecutive cases of muscle-invasive bladder cancer that received GC NAC followed by open RC (2000–2013). A cohort of 121 patients treated by RC alone was used for comparison. Pathologic response and cancer-specific survival (CSS) were compared. We created the Johns Hopkins Hospital Dose Index to characterize chemotherapeutic dosing regimens and accurately assess sufficient neoadjuvant dosing regarding patient tolerance.

Results—No significant difference was noted in 5-year CSS between GC NAC (58%) and non-NAC cohorts (61%). The median follow-up was 19.6 months (GC NAC) and 106.5 months (non-NAC). Patients with residual non-muscle-invasive disease after GC NAC exhibit similar 5-year CSS relative to patients with no residual carcinoma ($P = 0.99$). NAC pR (pT1) demonstrated improved 5-year CSS rates (90.6% vs. 27.1%, $P < 0.01$) and decreased nodal positivity rates (0% vs. 41.3%, $P < 0.01$) when compared with nonresponders (pT2). Clinicopathologic outcomes were inferior in NAC pathologic nonresponders when compared with the entire RC-only-treated cohort. A lower pathologic nonresponder rate was seen in patients tolerating sufficient dosing of NAC as stratified by the Johns Hopkins Hospital Dose Index ($P = 0.049$), congruent with the National Comprehensive Cancer Network guidelines. A multivariate classification tree model demonstrated 60 years of age or younger and clinical stage cT2 as significant of NAC response ($P < 0.05$).

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Conclusions—Pathologic nonresponders fare worse than patients proceeding directly to RC alone do. Multiple predictive models incorporating clinical, histopathologic, and molecular features are currently being developed to identify patients who are most likely to benefit from GC NAC.

Keywords

Urothelial carcinoma; Bladder cancer; Neoadjuvant chemotherapy; Gemcitabine-cisplatin; Pathologic response

1. Introduction

Neoadjuvant cisplatin-based chemotherapy (NAC) in combination with radical cystectomy (RC) for the treatment of muscle-invasive bladder cancer (MIBC) is supported by level 1 evidence [1–4]; however, it remains underutilized nationally [5,6]. Methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) is an established standard neoadjuvant regimen [1]. Dose-dense MVAC (DD-MVAC) [7] and gemcitabine plus cisplatin (GC) [8] have demonstrated similar overall survival rates when compared with those of MVAC in patients with metastatic urothelial carcinoma (UC). Although no definitive evidence demonstrates superiority of GC over MVAC, GC has increasingly been used in the NAC setting because of a more favorable side effect profile.

The National Cancer Database reported increasing use of NAC, from 10.2% in 2006 to 20.9% in 2010 [9]. Almost 80% of the Bladder Cancer Advocacy Network oncologists offer NAC with GC, which is the most used regimen (90%), followed by MVAC (30%) and DD-MVAC (20%) [10]. A prospective multicenter abstract of Bladder Cancer Advocacy Network investigators identified a 47% cisplatin-based neoadjuvant regimen utilization rate [11]. Despite its widespread use, there is a paucity of data assessing long-term patient outcomes following neoadjuvant GC.

To evaluate the effect of GC NAC on long-term outcomes and identify clinical parameters predictive of response, we present the largest single-institution, retrospective study of solely GC NAC-treated patients. Pathologic response and cancer-specific survival (CSS) were compared with a series of RC-only-treated patients over a similar period at our institution.

2. Materials and methods

2.1. Patient cohorts

The Johns Hopkins Hospital (JHH) Institutional Review Board–approved (N0:03-03-07-02d) bladder cancer database was queried to identify all patients who received any NAC followed by open RC between 2000 and 2013. Only patients who underwent open RC following GC NAC were included in the study; all other forms of NAC were excluded. GC regimens that were assessed included (1) the traditional 1,000 mg/m² of gemcitabine on days 1, 8, and 15 along with 70 mg/m² of cisplatin on day 1 of a 28-day cycle for 3 to 4 cycles, (2) 1,000 mg/m² of gemcitabine on days 1 and 8 along with 70 mg/m² of cisplatin on day 1 of a 21-day cycle for 4 cycles, or (3) 1,000 mg/m² of gemcitabine and 35 mg/m² of cisplatin given on days 1 and 8. Each NAC patient underwent a prechemotherapy staging

computed tomography or magnetic resonance imaging. Following NAC, a restaging examination was performed within 1 month before RC, comprising diagnostic cystoscopy without transurethral resection [12] and computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis. NAC patients with clinical node-positive disease (before or after chemotherapy) were included if their disease was deemed surgically resectable or lymph node (LN) enlargement was confined to the pelvis.

Consecutive MIBC patients treated by RC alone (non-NAC) beginning in the year 2000 were identified and used for comparison. These patients were either not offered NAC, as it was not currently standard of care at our institution during that period, or chose not to pursue NAC. Patients with unknown follow-up or cause of death were excluded. These 2 cohorts did not differ significantly regarding clinical stage (cStage), age, clinical nodal stage, and smoking status. All patients underwent preoperative imaging, and all non-NAC patients with LN disease/metastasis were excluded and recommended to receive systemic chemotherapy, unless deemed surgically resectable. Pelvic lymphadenectomy followed a standard surgical template including LN of the obturator fossa and those along the internal and external iliac arteries up to and including the common iliac artery and vein.

2.2. Response and survival evaluations

All post-NAC cystectomy pathologic evaluations were performed at JHH by expert pathologists. We defined NAC pathologic responders (pR) as the absence of residual MIBC (pT1) at the time of RC [13]; pathologic nonresponders (pNR) were defined by the presence of muscle-invasive, extravesical, and metastatic disease (pT2). CSS was defined according to review of death certificates by the JHH Cancer Registry or biopsy of metastatic lesions confirming UC and was updated for all patients by review of clinical medical records and query of the Social Security Death Database. For cases without evidence of cancer-specific death, survival was censored at the date of last clinic visit.

2.3. JHH dose index

According to the National Comprehensive Cancer Network 2014 guidelines, MIBC patients should receive 4 cycles of neoadjuvant GC. However, patients commonly have missed/held doses or fail to complete treatment cycles owing to intolerance, renal impairment, or hematological complications [14]. Currently, no standardized terminology exists within the genitourinary oncology literature to classify the amount of NAC received when interpreting pR to a given therapeutic modality. As RCTs assessing NAC used 3-cycle MVAC regimens, 3 or 4 cycles are regarded as adequate therapy [15]. The effect of missed or reduced doses is not accounted for when assessing true pR. We created the JHH Dose Index (JHH-DI) to characterize patient tolerance to NAC (Table 1). The medical record review that was performed for all patients receiving NAC determines dosing amount and total number of cycles received. Dose reduction was defined as a reduction in either gemcitabine or cisplatin dose owing to patient intolerance. Each patient was given a dose index score summarizing the total amount of chemotherapy tolerated.

2.4. Statistical analysis

Univariate tests of association between baseline age, gender, race, cStage, clinical nodal stage, and pR to NAC were conducted using the Fisher exact, Goodman-Kruskal, and Kruskal-Wallis tests, where appropriate. One-tailed Fisher exact test was used for the JHH-DI, investigating whether a patient receiving less NAC owing to intolerance is more likely to not exhibit a pR. Kaplan-Meier analysis by log-rank test was used to illustrate CSS comparisons. Statistically significant variables ($P < 0.05$) by univariate analyses were used in multivariate analyses, including multivariate logistic regression and multivariate classification tree, to stratify the GC NAC cohort according to pR. All analyses were conducted using MATLAB version 8.3.0.532 (The Mathworks, Inc., Natick, MA).

3. Results

3.1. Patient demographics

A total of 417 patients underwent RC for MIBC between 2000 and 2013. The NAC utilization rate was 52.5% (219 patients), and GC was administered in 150 (68.5%). Preoperative imaging in the GC NAC cohort revealed 137 clinical pelvic node-negative patients and 13 node-positive patients. Only those patients with enlarged LN in the obturator fossa and below the common iliac artery and vein were included in this analysis. Of the 198 non-NAC MIBC patients, a cohort of 121 consecutive patients treated between 2000 and 2005 was used for comparison (77 patients were excluded for incomplete medical record data and follow-up information). No significant difference was noted between the 2 cohorts regarding preoperative clinical parameters (Table 2).

3.2. Pathologic outcomes of GC NAC and non-NAC cohorts

A 53% pR rate (pT1) in the NAC population was seen compared with 26% within the non-NAC cohort ($P < 0.01$). Nodal metastases were decreased to 18.1% in the NAC cohort compared with 26.3% in the non-NAC cohort ($P = 0.13$) (Table 3). Lymphadenectomy was not performed because of adhesions in 15 patients (8 GC NAC and 7 non-NAC). The mean number of LNs removed was 17 ± 0.77 (range: 1–46) in the NAC patients, and in the non-NAC, the mean number of LNs removed was 14.9 ± 0.87 (range: 1–57). Within the NAC cohort, no nodal metastases were identified in 79 pR patients, whereas the remaining 63 pNR patients demonstrated a 41% positive node rate.

3.3. Cancer-specific survival outcomes of GC NAC and non-NAC cohorts

Median follow-up for the NAC and non-NAC cohorts were 19.6 and 106.5 months, respectively. The 5-year CSS for the entire NAC and non-NAC cohorts were 58% (95% CI: 46.4%–69.5%) and 61% (95% CI: 51.6%–69.9%), respectively (Fig. 1A). No difference was noted in CSS between NAC and non-NAC cohorts when stratified by organ-confined cStage (cT2, $P = 0.96$; cT3/4, $P = 0.42$). Furthermore, no significant effect of NAC was noted in multivariate Cox proportional hazards modeling of CSS incorporating cStage across both the cohorts ($P = 0.33$) (Table 4).

3.4. Cancer-specific survival outcomes according to pR strata

NAC patients with residual non-muscle-invasive disease (pTis, pTa, and pT1) experienced similar CSS to those of NAC complete responders at cystectomy (pT0) ($P = 0.99$, Fig. 1B). None of these pathologic responders experienced nodal metastases (Table 3). The NAC pR (pT1) demonstrated improved CSS when compared with NAC pNR (pT2), 90.6% vs. 27.1%, $P < 0.01$ (Fig. 1B). NAC pR exhibited improved CSS when compared with the entire non-NAC cohort ($P < 0.01$, Fig. 1B). Although NAC pNR fared worse than the non-NAC cohort did ($P < 0.01$, Fig. 1B), these findings were independent of cStage by multivariate Cox proportional hazard modeling.

3.5. Sufficiency of therapy (JHH-DI) in relation to pR

Approximately 83% of patients were able to tolerate a sufficient dosing of NAC therapy (JHH-DI ≥ 2), corresponding with a pR rate of 57%, which is significantly higher than the 36% pR rate for patients receiving less sufficient therapy (JHH-DI < 2) (1-tailed $P = 0.049$, Table 5). The JHH-DI was not included in subsequent multivariate modeling, as it would not be available during the clinical decision to treat with NAC.

3.6. Clinical parameters associated with response to GC NAC

Older than 60 years at cystectomy and cStage $> cT2$ were significantly associated with nonresponse to NAC ($P < 0.05$) on univariate analysis, and gender, race, and clinical LN status were not associated with it (Table 6). On multivariate logistic regression analysis, both age at cystectomy and cStage were independent predictors of nonresponse to GC NAC.

These 2 clinical variables were incorporated in a multivariate classification tree analysis to identify a clinical algorithm stratifying patients on the likelihood of benefit from NAC. The decision points were based on (1) the presence or absence of clinically organ-confined disease and (2) older than 60 years at cystectomy (Fig. 2A). A significant difference exists in NAC pNR rates for cT2/60 years of age or younger when compared with $> cT2$ /older than 60 years (23% and 73%, respectively). The other 2 terminal branches (2_a and 2_b in Fig. 2A) were combined into an intermediate group because of similar pNR rates (49% and 55%, respectively). There was no significant difference in NAC dosing intensity across these patient groupings, as characterized by the JHH-DI.

Cox proportional hazard modeling using the classification tree-derived groupings as an ordinal predictor variable shows a significant association with 5-year CSS in the GC NAC cohort (Fig. 2B). There is an approximate doubling of the risk of CSS failure when comparing groupings (hazard ratio = 1.9, 95% CI: 1.2–2.9). Importantly, no significant differences in 5-year CSS are observed when these groupings are applied to the non-NAC cohort (Fig. 2C), which indicates that a high risk of nonresponse to GC NAC (i.e., group 3) does not simply equate to more aggressive disease. When comparing these 3 patient groupings across both the GC NAC and the non-NAC cohorts, in group 3 (cT > 2 and older than 60 years), we observed a decrease in CSS with GC NAC vs. cystectomy alone, which approaches statistical significance (log-rank $P = 0.08$). This finding would suggest that this patient stratum with a high risk of NAC nonresponse may fare better with cystectomy alone; however, these findings must be validated with more patients and in a multi-

institutional study. Moreover, the ongoing development of molecular markers of NAC nonresponse will likely yield better resolution of this patient stratum.

4. Discussion

Level 1 evidence exists supporting the use of MVAC NAC followed by RC to improve survival compared when with RC alone [1]. However, GC has improved patient tolerance and demonstrated similar efficacy in metastatic disease [4]. At Johns Hopkins, 69% of all NAC patients received GC, consistent with national practice patterns [5,6]. The National Comprehensive Cancer Network guidelines suggest 3 to 4 cycles of NAC for survival benefit [13]; however, some patients require dose reduction or held doses [7]. We created the JHH-DI to provide an objective measurement of chemotherapy tolerance for correlation with pR. Patients with a JHH-DI < 2 were significantly more likely to be a pNR compared with those tolerating greater therapy (JHH-DI ≥ 2 , $P = 0.049$). Patients tolerating more NAC dosing demonstrated pR rates of $>50\%$, which highlights the importance of characterizing NAC dosing in the context of accurately defining pR to NAC.

This report represents the first study, to our knowledge, discerning the tolerability of GC NAC in conjunction with pathologic outcomes, leading to the creation of the JHH-DI. Our data support the more recent definition of NAC responder (pT1) [13,16]. A previous study suggested worse overall survival in MVAC NAC patients with residual pTa, pTis, or pT1 when compared with that in pT0 patients [17]. However, in this prior study, the far superior outcomes of all patients with $< pT2$ stage established residual non-muscle-invasive disease as a significantly meaningful pathologic benchmark in the NAC setting. Our study shows that residual pTa, Tis, or pT1 disease after GC NAC had similar CSS to that of pT0 patients ($P = 0.99$). Down staging to pT1 in the GC NAC cohort is more likely because of treatment effect and not aggressive transurethral resection, as we do not perform resection during restaging cystoscopy following NAC [12]. The rates of down staging were much higher in the NAC group (53% vs. 26%, $P < 0.01$). Stratification of the GC NAC cohort by responder status demonstrates markedly different survival, with pR exhibiting outstanding CSS ($>90\%$ at 5 y) and pNR exhibiting markedly inferior CSS ($<30\%$ at 5 y). This difference is driven by the absence of LN metastases in NAC pR. Importantly, NAC pNR demonstrated inferior CSS to non-NAC, suggesting those patients may be better served by RC alone.

The Cancer Genome Atlas has allowed for greater understanding of molecular characterizations involved in UC [18]. The alterations may indicate possible therapeutic targets and lead to biomarker identification and predictive models, allowing assessment of chemoresponsiveness [19]. Our simple predictive model identifies patients with a high likelihood of achieving pR to help guide usage of GC NAC. A significantly higher rate of pR was seen in patients with cT2 stage disease than in patients with cT3/cT4 stage disease (50% vs. 27%, respectively). This emphasizes the importance of GC NAC use in clinically organ-confined MIBC, as these patients derive the highest benefit of cancer-free survival. Multivariate classification tree analysis using age at cystectomy and clinical T stage (Fig. 2A) identified patient strata with pNR rates of 73%, 52%, and 23%. This should better guide the use of NAC toward patients who are most likely to derive a benefit and identify patients who can be better managed by cystectomy alone. For each group increment in the

classification tree, there was an approximate 2-fold increased risk of cancer-specific mortality. The implication exists that patients with higher cStage and older age fare worse; however, this is not seen when assessing the non-NAC cohort. Therefore, to optimize patient selection with the most to benefit from NAC, our data support NAC in patients with organ-confined disease (cT2) and aged 60 years or younger.

Additional characterization of histomorphology, subtypes of invasive UC, and somatic mutation profiles is required to obtain higher predictive accuracy for the identification of patients who are not likely to derive benefit from GC NAC. NAC utilization rates remain low despite randomized trials demonstrating an overall survival benefit. Better predictive models may help increase NAC utilization rates and improve physician adherence to the current guideline recommendations.

Our study is limited in that it represents a single-institution retrospective study without randomization, has relatively short follow-up, and may harbor potential bias including practice patterns and selection of patients receiving NAC. Additionally, the effect of variant histology on NAC intensity and outcomes was not evaluated. Our proposed JHH-DI is an attempt toward a standardized method for the characterization of NAC tolerance in MIBC; further studies are needed to validate these findings. Although this study represents NAC patients solely receiving GC, the results may vary when assessing patients undergoing MVAC NAC. A large, multicenter, international study of 935 patients identified no significant difference in pT0 rates between patients receiving GC or MVAC on multivariate analysis ($P = 0.6$) [20]. Additionally, the utility of DD-MVAC has been shown in the adjuvant metastatic setting for UC [7]; however, emerging evidence is validating its use in the neoadjuvant setting [15,21]. The effect of adjuvant or salvage chemotherapy was not assessed; however, further investigation into the effect of adjuvant and salvage chemotherapy following NAC in both LN- and LN+ disease is warranted. Finally, we are working toward multicenter, international validation of the clinical classification tree in order to confirm our findings, and until this has been established, we cannot recommend change in practice patterns.

5. Conclusions

Pathologic responders to GC NAC should include patients with residual pTis, pTa, and pT1 disease as they demonstrate comparable 5-year CSS to pT0 patients. Non-responders have worse CSS than that of patients proceeding directly to RC alone, and it is suggested that further studies are needed to identify those who may not benefit from GC NAC. A clinical predictive model based on age and cStage can identify 3 patient strata with approximately a 75%, 50%, and 25% chance of not responding to GC NAC. Implementation of such an approach, once independently validated, would better guide the use of GC NAC. The development and incorporation of the relevant molecular and histopathologic factors into such a model is likely to augment it and ultimately generate highly clinically actionable data.

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Fig. 1.

(A) The 5-year CSS for GC NAC and non-NAC RC-alone cohorts, no significant difference by log-rank test was observed, $P = 0.18$. (B) The 5-year CSS for the GC NAC cohort stratified by pathologic stage relative to the 5-year CSS for non-NAC. The 5-year CSS for ypT0 is equivalent to that for pTis, pTa, pT1; therefore, responders to GC NAC were defined as pT0 and residual pTa, pTis, and pT1, as has been previously reported. The 5-year CSS for GC NAC responders, GC NAC nonresponders, and the non-NAC cohort are all statistically different from each other by log-rank test, $P < 0.01$.

Fig. 2.

(A) Using clinical T stage and age at cystectomy in classification tree analysis resulted in stratification of the NAC cohort to 3 grouping as shown. GC NAC pNR was highly correlated with these groupings by the Fisher exact test but adequacy of therapy was not. (B) The 5-year CSS for the GC NAC cohort is significantly stratified by the classification tree model from (A). (C) By contrast, no significant stratification of the 5-year CSS for the non-NAC cohort is observed when the classification tree model is applied to this cohort.

Table 1

The Johns Hopkins Hospital Dose Index designed to characterize the amount of NAC received by patients before RC and how this affects the determination of pathologic response status

JHH-DI	Definition
3	4 Cycles without dose reduction or held doses
2	4 Cycles with dose reduction or 3 cycles no dose reduction
1	3 Cycles with dose reduction or 2 cycles no dose reduction
0	<2 Cycles

Table 2

Patient preoperative clinical demographics based on cohort group. No statistically significant differences across the cohorts were identified

Demographic	GC NAC	non-NAC	<i>P</i> value
Number of patients	150	121	—
Age at cystectomy (median; range)	62.5; 39–82	63.7; 34–88	0.08
Gender			0.88
Male	82%	82%	
Female	18%	18%	
Race			0.17
White	95%	90%	
Nonwhite	5%	10%	
Clinical T stage			0.12
cT1	0%	1%	
cT2	65%	74%	
cT3	25%	21%	
cT4	10%	4%	
Clinical N stage			0.06
N0	91%	98%	
N/M+	9%	2%	

Table 3

Pathologic outcomes based on cohort group

Demographic	GC NAC (n = 150)	non-NAC (n = 121)
Pathologic T stage		
pT0	23%	7%
pTis and Ta	19%	12%
pT1	11%	7%
pT2	13%	19%
pT3	23%	45%
pT4	11%	10%
Pathologic N stage		
pN0	82%	74%
pN+	18%	26%
Nodal metastasis rate stratified by pT stage		
pT1	0% (0/79)	3% (1/31)
pT2	41% (26/63)	35% (29/83)

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Table 4
Response spectrum for organ-confined disease vs. extravesical disease based on clinical staging in the GC/NAC and non-NAC cohorts

Organ confined (cT2)	GC/NAC, n = 98	non-NAC, n = 90	Extravesical disease (cT3–cT4)	GC/NAC, n = 52	non-NAC, n = 31
pR (pT1)	63%	30%	pR (pT1)	35%	16%
pNR (pT2)	37%	70%	pNR (pT2)	65%	77%

Table 5

Johns Hopkins Hospital Dose Index stratified according to pathologic response to chemotherapy

GC NAC stratum	JHH dose index	
	Adequate (≥ 2), n = 124	Inadequate (<2), n = 26
pR (ypT1)	57%	36%
pNR (ypT2)	43%	64%

Univariate and multivariate logistic regression analyses identify age and clinical stage as independent predictors of nonresponse to GC NAC

Table 6

Variable	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age, y (>60 vs. ≤60)	2.76	1.42–5.39	0.003	2.81	1.40–5.64	0.004
Gender (male vs. female)	<i>0.50</i>	0.21–1.15	0.102			
Race (white vs. other)	<i>1.49</i>	0.34–6.47	0.595			
Clinical T stage (>cT2 vs. ≤cT2)	3.25	1.61–6.57	0.001	3.31	1.60–6.85	0.001
Clinical N stage (cN+ vs. cN0)	<i>1.19</i>	0.37–3.89	0.769			

Bold values indicate statistical significance.

OR = odds ratio.