Original Article

# Predictors of pathologic response to neoadjuvant chemotherapy in muscle-invasive bladder cancer

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## Abstract

**Objective:** To identify factors that could predict pathologic response to neoadjuvant (NAC) therapy in muscle invasive bladder cancer (MIBC) patients and report the impact of NAC on the risk of perioperative complications after radical cystectomy at our institution.

**Materials and Methods:** We reviewed the hospital database from January 2014 to March 2021 for MIBC patients who received NAC prior to radical cystectomy (RC). All patients were divided into a responder (pT ≤ T1) or non-responder group (> pT2). Data was analyzed to determine the factors associated with pathologic response to NAC. A subgroup analysis of the gemcitabine and carboplatin (GCb) regimens was also carried out.

**Results:** Out of the 50 patients who met the inclusion criteria, 13 (26%) were categorized as responders and 37 (74%) as non-responders. With regard to NAC variables, 12 patients (24%) received cisplatin-based NAC, and 38 patients (74%) received GCb. From the multivariate analysis, pretreatment hemoglobin (Hb) > 12 g/dl (OR 16.42, 95% CI 1.78-151.86, p = 0.01) and neutrophil-to-lymphocyte ratio (NLR) < 3 (OR 12.81, 95% CI 1.36-120.9, p = 0.03) were associated with significantly increased odds of pathologic response, while tumor size < 4 cm (OR 12, 95% CI 1.92-75.05, p = 0.008) was associated with significantly increased odds of pathologic response in the subgroup analysis.

**Conclusions:**Pretreatment Hb and NLR were independently associated with pathologic response to NAC. For MIBC patients who are cisplatin ineligible, GCb followed by RC may be the recommended treatment, particularly in those with tumors less than 4 cm in size. In addition, administering NAC prior to RC does not increase the risk of perioperative complications.

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## Introduction

Muscle-invasive bladder cancer (MIBC) is an aggressive disease that has mortality rates far higher than non-muscle-invasive bladder cancer (NMIBC); approximately 85% of untreated MIBC patients died within 2 years.[1] Radical cystectomy (RC) and pelvic lymphadenectomy (PLND) were formerly the mainstay of treatment for MIBC patients but subsequently, the use of neoadjuvant chemotherapy (NAC) followed by RC and PLND has been supported by numerous randomized clinical trials and meta-analyses, which have found a 6% survival benefit at 10 years.[2-5] For this reason, the current treatment guidelines recommend NAC as a standard treatment for nonmetastatic MIBC.[6-8]

As a result of the Southwest Oncology Group (SWOG) 8710 trial, Grossmann et al. demonstrated significant improvement in pathologic complete response (pCR) (38% vs 15%; $p < 0.001$) and median overall survival (77 vs 46 months; $p = 0.05$) in patients treated with NAC compared to those treated with cystectomy alone.[2] The survival benefit of NAC was shown to be strongly associated with downstaging of the tumor to pCR.[2,9-13] Interestingly, patients treated with NAC which resulted in residual non-muscle invasive cancer including carcinoma in situ (CIS), pTa, and pT1 disease also showed no statistically significant difference in overall survival, compared to pCR patients.[10,11,13-15] Recently, there have been efforts to develop prognostic tools that allow the selection of patients likely to respond to NAC. Many predictive factors have been investigated, but none have been validated for routine use in clinical practice.[16]

Several chemotherapy regimens have been used for treatment of MIBC, most of which included a cisplatin-based regimen due to evidence of better outcome. Despite the effectiveness of cisplatin-based chemotherapy, its toxicity profile, especially severe renal toxicity, makes it unsuitable for patients with renal dysfunction. In addition, patients with TCC are often elderly, with frequent concomitant diseases, in particular, clinical or subclinical renal function impairment. A gemcitabine and carboplatin (GCb) combination regimen, which has a considerably lower toxicity profile, has been reported to play a potential role in cisplatin ineligible advanced bladder cancer patients in many studies.[17-23] However, in the neoadjuvant setting, there is only limited evidence from a few centers that supports the use of the GCb regimen in MIBC patients in whom cisplatin is unsuitable.[20,24-26] Our institution, King Chulalongkorn Memorial Hospital (KCMH), is one of the centers that also commonly uses GCb as alternative treatment in cisplatin-unsuitable patients. To date, there is no clear evidence to support the inferiority of a carboplatin-based regimen against a cisplatin-based one in a neoadjuvant setting.

Therefore, the objective of this study was to determine the clinicopathologic factors that could predict the pathologic response to NAC in order to improve the selection of patients who would benefit from chemotherapy prior to cystectomy and to evaluate a subgroup analysis of GCb regimen from our institution. Additionally, we aimed to report the impact of NAC on the risk of perioperative complications after RC at our institution.

## Materials and Methods

### Patients

The study was retrospective in design and we reviewed the records of all 60 consecutive patients treated with neoadjuvant chemotherapy before undergoing RC and bilateral pelvic lymphadenectomy at King Chulalongkorn Memorial Hospital from January 2014 to March 2021. Patients were included if they had MIBC (> T2) that was feasible for RC and were excluded if they had not completed at least two cycles of NAC, received preoperative radiotherapy for MIBC, or had predominant squamous or adenocarcinoma components or any small cell components. The study protocol was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University (IRB number 089/64)

### Study measures, definitions, and outcomes

Demographic data including age, gender, body mass index (BMI), and underlying medical conditions were collected. Clinical data and parameters including smoking and alcohol drinking status, hemoglobin (Hb) and serum creatinine at first visit, radiological evidence of hydronephrosis, size of bladder tumor and neutrophil-to-lymphocyte ratio (NLR) were also collected. Histopathologic reviews of the transurethral resection of bladder tumor (TURBT) specimens and cystecto-

my specimens were completed by the pathologists at our institution. Clinical staging was based on TURBT and preoperative cross-sectional imaging including computed tomography (CT) imaging and magnetic resonance imaging (MRI).

At our institution, the main cisplatin-based NAC regimens that have been used for treating MIBC patients included gemcitabine and cisplatin (GCp), and cisplatin, methotrexate, and vinblastine (CMV). In addition to standard regimens, we also used gemcitabine and carboplatin (GCb) as a first-line treatment regimen in the patients who were unfit for cisplatin-based chemotherapy. The decision regarding NAC regimens was made solely by our oncologists in accordance with the need determined by the patient's clinical status. During NAC administration, chemotherapy toxicities were routinely monitored in the oncology outpatient clinic. Presence of any adverse events associated with the chemotherapy would usually lead to individual regimen adjustment, ranging from a decrease in NAC dosage to a change of regimen. The NAC variables included types of regimens, number of cycles, time from TURBT to NAC, and time from end of NAC to RC.

After the full therapeutic course, the chemotherapy response was evaluated with cross-sectional imaging, and subsequently, resectable cases underwent surgery. Intra- and post-operative variables were collected, specifically operative time, estimated blood loss (EBL), total blood transfusion, and anesthetic record. Perioperative complications were recorded for the first 30 days after surgery. All perioperative complications were classified in accordance with Clavien-Dindo system as either minor (grade < 2) or major (grade > 3A).[27]

All patients were divided into 2 groups based on final histopathologic findings at cystectomy: a responder group including those with a pathologically noninvasive downstaging or a pathologic partial response (pPR), defined as pTis/pTa/pT1 and those with pathologic complete response (pCR), defined as no residual tumor in cystectomy specimen (pT0) and a non-responder group, defined as > pT2. The primary outcome of interest was identification of predictive factors associated with pathologic downstaging and pathologic complete response to NAC. In addition, specific interpretation of the subgroup analysis of GCb regimen was carried out. Secondary outcome was focused on perioperative complications associated with RC after receiving NAC, as defined in accordance with the Clavien-Dindo system as described above.

**Statistical analyses**

Demographic and clinical data were collected and described for all included patients. Continuous variables are expressed as median (interquartile range: IQR) and percentage for categorical variables. Differences in continuous and categorical variables between two groups were assessed using a Wilcoxon rank sum test and Chi-square test or Fisher's exact test, respectively. Logistic regression was used to determine the factors associated with pathologic response to NAC. Multivariate models were developed by adjusting for covariates with $p < 0.1$ in univariate models and a stepwise backward LR to select the final model. All p-values reported are two-sided. Statistical significance was defined as $p < 0.05$. Stata version 15.1 (Stata Corp., College Station, Texas) was used for analysis.

## Results

**Patient demographics and clinical characteristics**

During the study period, a total of 60 patients who received neoadjuvant chemotherapy before undergoing RC at our institution were included in the study. Of these, 50 patients (83.3%) fulfilled the inclusion and exclusion criteria of the study.

Baseline characteristics and pathologic features between the responder and non-responder groups are summarized in Table 1. The median age of the population was 69 years (IQR, 44-87 years), with the number of males predominating (64%). Of the 50 patients, 14 (28%) were cT2 disease, 25 (50%) had cT3 disease, and 11 (22%) had cT4 disease. Lymph node involvement (cN+) was found in 11 (22%) patients, and M1a disease in 4 (8%).

Of all 50 patients who received NAC prior to RC, 13 patients (26%) were grouped into responders and 37 patients (74%) were non-responders. In the responder group, 5 (10%) were pCR (pT0), and 8 (16%) were non-invasive downstaging or pPR (pTis/pTa/pT1). There were no significant differences in age, gender, ECOG performance status, clinical T stage, and histologic type between two groups. Conversely, there was a statistically significant difference in the presence of lymphovascular invasion (LVI) between the two groups, with none of the responder patients having LVI.

**Table 1.** Clinical characteristics and pathologic features stratified by treatment response

| Characteristics | Total (N = 50) | Non-responder (N = 37) | Responder (N = 13) | P-value |
|---|---|---|---|---|
| Male, n (%) | 32 (64) | 24 (64.9) | 8 (61.5) | 0.83 |
| Age, years mean (SD) | 67.4 (9.8) | 68.6 (9.5) | 64 (10.2) | 0.15 |
| BMI (kg/m$^2$), mean (SD) | 24 (4) | 23.4 (3.9) | 25.5 (4.3) | 0.11 |
| Smoker, n (%) | 25 (50) | 17 (46) | 8 (61.5) | 0.33 |
| Alcohol drinking status, n (%) | 22 (44) | 15 (40.5) | 7 (53.9) | 0.41 |
| Diabetes mellitus (DM), n (%) | 12 (24) | 10 (27) | 2 (15.4) | 0.40 |
| Hypertension (HT), n (%) | 35 (70) | 26 (70.3) | 9 (69.2) | 0.94 |
| Hb at first visit (g/dl, mean (SD) | 10.7 (1.4) | 10.6 (1.4) | 11 (1.6) | 0.36 |
| ECOG performance status, n (%) | | | | 0.06 |
| - 0 | 11 (22) | 6 (16.2) | 5 (38.5) | |
| - 1 | 38 (76) | 31 (83.8) | 7 (53.9) | |
| - 2 | 1 (2) | 0(0) | 1 (7.7) | |
| eGFR at first visit (ml/min/1.73 m$^2$), median (IQR) | 66.6 (54-81.2) | 65 (50.7-80) | 77.4 (60.5-87.1) | 0.21 |
| Presence of hydronephrosis, n (%) | 25 (50) | 22 (59.5) | 3 (23.1) | 0.02 |
| Histologic type (TURBT), n (%) | | | | 0.026 |
| - Pure TCC | 41 (82) | 29 (78.4) | 12 (92.3) | |
| - Others | 9 (18) | 8 (21.6) | 1. (7.7) | |
| Clinical T stage at diagnosis, n (%) | | | | 0.37 |
| - T2 | 14 (28) | 9 (24.3) | 5 (38.5) | |
| - T3 | 25 (50) | 18 (48.7) | 7 (53.9) | |
| - T4 | 11 (22) | 10 (27) | 1 (7.7) | |
| Tumor size (cm), median (IQR) | 4.2 (3.5-5) | 4.6 (3.9-5.7) | 2.9 (2-3.8) | 0.001 |
| Grossly complete resection | 12 (29.3) | 5 (16.7) | 7 (63.6) | 0.003 |
| NAC Regimens | | | | 0.16 |
| - Gemcitabine / Carboplatin (GCb) | 38 (74) | 30 (81.1) | 8 (61.5) | |
| - Cisplatin-based NAC (CMV, and GCp) | 12 (24) | 7 (18.9) | 5 (38.5) | |
| Number of NAC cycles, mean (SD) | 3.6 (1.1) | 3.8 (1.1) | 3.3 (0.9) | 0.19 |
| Time from TURBT to NAC (day), median (IQR) | 34 (23-72) | 31.5 (21-50) | 50 (30-81) | 0.10 |
| Time from TURBT to RC (day), median (IQR) | 165 (128-211) | 154 (122-208) | 168 (145-229) | 0.57 |
| Time from end of NAC to RC (day), median (IQR) | 42 (32-61) | 42.5 (32-62) | 41 (32-58) | 0.72 |
| Presence of LVI, n (%) | 22 (44) | 22 (59.5) | 0 (0) | <0.001 |
| Positive surgical margin from RC specimen, n (%) | 4 (8) | 4 (10.8) | 0 (0) | 0.59 |
| Neutrophil to lymphocyte ratio (NLR), median (IQR) | 2.84 (2.04-3.68) | 3.15 (2.11-4.6) | 2.07 (2-2.6) | 0.01 |
| Operative time (min), median (IQR) | 353 (307-417) | 350 (300-410) | 415 (322-450) | 0.12 |
| Total estimated blood loss (ml), median (IQR) | 950 (700-1600) | 900 (700-1600) | 1100 (800-1350) | 0.83 |

N = patient number, BMI = body mass index, Hb = hemoglobin, ECOG = Eastern Cooperative Oncology Group, NAC = neoadjuvant chemotherapy, RC = radical cystectomy, SD = standard deviation, IQR = interquartile range, TURBT = transurethral resection of bladder tumor, LVI = lymphovascular invasion

Regarding NAC variables, 12 patients (24%) received cisplatin-based NAC (GCp and CMV), and 38 patients (74%) received GCb. There were no significant differences in NAC regimens, number of NAC cycles, time from TURBT to NAC, and time from end of NAC to RC between two groups.

The pCR rates for the cisplatin-based NAC were 25% (3 of 12 patients) which were higher than GCb regimen (5.26%, 2 of 38 patients). The pPR rates for the cisplatin-based regimens and GCb regimen were 16.67% (2 of 12 patients) and 15.79% (6 of 38 patients), respectively. Positive surgical margins were reported in 4 patients (8%)

**Table 2.** Factor associated with pathologic response

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | P-value | aOR (95% CI) | P-value |
| Male sex | 0.87 (0.23-3.2) | 0.83 | | |
| Age < 60 years | 4 (0.93-17.25) | 0.06 | | |
| Smoker, n (%) | 1.88 (0.52-6.84) | 0.34 | | |
| Alcoholic drinking status | 1.71 (0.48-6.11) | 0.41 | | |
| Presence of DM | 0.49 (0.09-2.61) | 0.4 | | |
| Presence of HT | 0.95 (0.24-3.76) | 0.94 | | |
| Histologic type: pure TCC | 0.3 (0.03-2.69) | 0.28 | | |
| Grossly complete resection | 8.75 (1.84-41.61) | 0.01 | | |
| Hb at first visit >12 g/dl | 22.15 (2.58-189.95) | 0.01 | 16.42 (1.78-151.86) | 0.01 |
| eGFR at baseline > 60 ml/min/1.73 $m^2$ | 2.03 (0.48-8.66) | 0.34 | | |
| Absence of hydronephrosis | 4.89 (1.15-20.79) | 0.03 | | |
| Tumor size < 4 cm | 4.98 (1.3-19.13) | 0.02 | | |
| cT stage | | | | |
| 2 | Ref | | | |
| 3 | 0.7 (0.17-2.83) | 0.62 | | |
| 4 | 0.18 (0.02-1.84) | 0.15 | | |
| GCb vs Cisplatin-based regimens | 2.27 (0.58-8.86) | 0.24 | | |
| Number of NAC cycle > 3 | 1.88 (0.52-6.84) | 0.34 | | |
| Neutrophil to lymphocyte ratio (NLR) < 3 | 15.75 (1.85-134.02) | 0.01 | 12.81 (1.36-120.9) | 0.03 |

DM = diabetic mellitus, HT = hypertension, Hb = hemoglobin, eGFR = estimated glomerular filtration rate, GCb = gemcitabine and carboplatin, NAC = neoadjuvant chemotherapy, CI = confidence interval, OR = odds ratio, aOR = adjusted odds ratio

which were found only in GCb regimen group. Then, the rate of positive surgical margins in GCb regimen group was 10.53% (4 of 38 patients).

**Factors associated with NAC response**

We demonstrated factors associated with pathologic response to NAC on table 2, and noticed that grossly complete resection (OR 8.75, 95% CI 1.84-41.61, p = 0.01), absence of hydronephrosis (OR 4.89, 95% CI1.15-20.79, p = 0.03), tumor size < 4 cm (OR 4.98, 95% CI 1.3-19.13, p = 0.02), NLR < 3 (OR 15.75, 95% CI1.1.85-134.02, p = 0.01) as well as hemoglobin (Hb) at first visit > 12 g/dl (OR 22.15, 95% CI 2.58-189.95, p = 0.01) were associated with significantly increased odds of pathologic response (< pT2). These factors were submitted to the multivariate analysis which we found that Hb at first visit > 12 g/dl (OR 16.42, 95% CI 1.78-151.86, p = 0.01) and NLR < 3 (OR 12.81, 95% CI 1.36-120.9, p = 0.03) were the independent variables in the pathologic downstaging and complete response to NAC.

In subgroup analysis, the total number of patients who received GCb regimen were 38. Eight patients (21.1%) were responders, while 30 (78.9%) were non-responders. Table 3 summarizes the baseline characteristics and pathologic aspects of the subgroup population. Contrast to the first analysis, we found that tumor size less than 4 cm (OR 12, 95% CI 1.92-75.05, p = 0.008) was the only parameter that associated with significantly increased odds of pathologic response (< pT2) on multivariate analysis (Table 4).

**Perioperative complications**

Data of perioperative complications in patients treated with NAC followed by RC are shown in table 5 and table 6. Seventy-five perioperative complications occurred in 42 patients (84%). Most of perioperative complications were minor (74%). There were only 5 major complications (10%), none of which were classified as grade 4 or 5. Anemia requiring blood transfusion (n = 32) and renal insufficiency (n = 14) were the most common minor complications. The median operative

**Table 3.** Clinical characteristics and pathologic features of patients receiving GCb regimen

| Characteristics | Total (N = 38) | Non-responder (N = 30) | Responder (N = 8) | P-value |
|---|---|---|---|---|
| Male, n (%) | 24 (63.2) | 19 (63.3) | 5 (62.5) | 0.97 |
| Age, years mean (SD) | 68.4 (9.5) | 69.3 (9.6) | 64.8 (8.6) | 0.23 |
| Smoker, n (%) | 21 (55.3) | 15 (50) | 6 (75) | 0.26 |
| Alcoholic drinking status, n (%) | 17 (44.7) | 12 (40) | 5 (62.5) | 0.43 |
| Diabetes mellitus, n (%) | 10 (26.3) | 9 (30) | 1 (12.5) | 0.65 |
| Hypertension, n (%) | 27 (71.1) | 22 (73.3) | 5 (62.5) | 0.67 |
| BMI, mean (SD) | 23.9 (3.8) | 23.5 (4.2) | 25.2 (1.2) | 0.25 |
| Hb at first visit, mean (SD) | 11.7 (2) | 11.4 (2.1) | 12.9 (0.9) | 0.04 |
| ECOG performance status, n (%) | | | | 0.20 |
| - 0 | 8 (21.1) | 5 (16.7) | 3 (37.5) | |
| - 1 | 30 (79) | 25 (83.3) | 5 (62.5) | |
| - 2 | 0 (0) | 0 (0) | 0 (0) | |
| eGFR at first visit (ml/min/1.73 $m^2$), median (IQR) | 68 (25.2) | 66.6 (27) | 73.5 (17) | 0.50 |
| Presence of hydronephrosis, n (%) | 21 (55.3) | 19 (63.3) | 2 (25) | 0.11 |
| Histologic type (TURBT), n (%) | | | | 0.31 |
| - Pure TCC | 31 (81.6) | 23 (76.7) | 8 (100) | |
| - Others | 7 (18.4) | 7 (23.3) | 0 (0) | |
| Clinical T stage at diagnosis, n (%) | | | | 0.23 |
| - cT2 | 11 (29) | 8 (26.7) | 3 (37.5) | |
| - cT3 | 18 (47.4) | 13 (43.3) | 5 (62.5) | |
| - cT4 | 9 (23.7) | 9 (30) | 0 (0) | |
| Tumor size (cm), median (IQR) | 4.4 (3.65-5.45) | 4.7 (4-5.8) | 2.6 (1.7-3.8) | 0.004 |
| Grossly complete resection, n (%) | 7 (24.1) | 4 (17.4) | 3 (50) | 0.13 |
| Number of NAC cycles, mean (SD) | 3.8 (1.1) | 3.9 (1.2) | 3.5 (0.9) | 0.43 |
| Time from TURBT to NAC (day), median (IQR) | 34.5 (23.5-80) | 31.5 (22.5-81.5) | 53.5 (29.5-76.5) | 0.35 |
| Time from TURBT to RC (day), median (IQR) | 169 (132-229) | 169 (128-229) | 169 (138.5-200) | 0.72 |
| Time from end of NAC to RC (day), median (IQR) | 41 (28-56) | 41 (28-62) | 40.5 (30-49) | 0.83 |
| Presence of LVI, n (%) | 20 (52.6) | 20 (66.7) | 0 (0) | 0.001 |
| Positive surgical margin from RC specimen, n (%) | 4 (10.5) | 4 (13.3) | 0 (0) | 0.64 |
| Neutrophil to lymphocyte ratio (NLR), median (IQR) | 2.9 (2.1-3.78) | 3.1 (2.1-4.6) | 2.3 (2-2.62) | 0.12 |

N = patient number, BMI = body mass index, Hb = hemoglobin, ECOG = Eastern Cooperative Oncology Group, NAC = neoadjuvant chemotherapy, RC = radical cystectomy, SD = standard deviation, IQR = interquartile range, TURBT = transurethral resection of bladder tumor, LVI = lymphovascular invasion

time (IQR), median estimated blood loss (IQR), median time to start soft diet (IQR), and median length of postoperative hospital stay (IQR) were 353 (307-411) minutes, 950 (700-1,600) ml, 7 (6-8) days, and 9 (8-12) days respectively.

## Discussion

The use of neoadjuvant cisplatin-based chemotherapy has been advocated for more than a decade since several prospective trials showed significant improvement in survival among MIBC patients compared with cystectomy alone.[2-5] Patients who meet a pCR after receiving NAC have excellent long-term overall survival as well as a pPR.[2,9-14] The results from our seven-year experiences revealed that pCR (25%) and pPR rates (16.67%) following cisplatin-based NAC were comparable to recent systematic reviews and meta-analyses.[28-30] For instance, according to the most recent meta-analysis, pCR was achieved in 16.6% (95% CI : 7.4-25.9%, I2 = 89.7%) patients and pPR was achieved in 14.6% (95% CI : 0.8-28.5%, I2 = 89.7%) patients.[28] Conversely, there was no systematic review or meta-analysis, but

**Table 4.** Factor associated with pathologic response in subgroup GCb regimen (N = 38)

| Characteristics | Total (N=38) | Non-responder (N = 30) | Responder (N = 8) | P-value |
|---|---|---|---|---|
| Male sex | 0.96 (0.19-4.84) | 0.97 | | |
| Age < 60 years | 5.4 (0.84-34.8) | 0.08 | | |
| Smoker | 3 (0.52-17.32) | 0.22 | | |
| Alcoholic drinking status | 2.5 (0.5-12.47) | 0.26 | | |
| Presence of DM | 0.33 (0.04-3.12) | 0.34 | | |
| Presence of HT | 0.61 (0.12-3.14) | 0.55 | | |
| eGFR at baseline > 60 ml/min/1.73 $m^2$ | 4.67 (0.51-42.92) | 0.17 | | |
| Absence of hydronephrosis | 5.18 (0.89-30.25) | 0.07 | | |
| Tumor size < 4 cm | 19 (1.89-190.92) | 0.004 | 12 (1.92-75.05) | 0.008 |
| Number of NAC cycle > 3 | 1.5 (0.31-7.19) | 0.61 | | |
| Neutrophil to lymphocyte ratio (NLR) < 3 | 8 (0.87-73.26) | 0.12 | | |

GCb = gemcitabine and carboplatin, DM = diabetic mellitus, HT = hypertension, eGFR = estimated glomerular filtration rate, NAC = neoadjuvant chemotherapy, CI = confidence interval, OR = odds ratio, aOR = adjusted odds ratio

**Table 5.** Perioperative complications classified by Clavien Classification (N = 50*)

| Clavien-Dindo classification | N (%) |
|---|---|
| No complication | 8 (16) |
| Complication | 42 (84) |
| - Grade 1 | 6 (12) |
| - Grade 2 | 31 (62) |
| - Grade 3a | 2 (4) |
| - Grade 3b | 3 (6) |
| - Grade 4a | 0 (0) |
| - Grade 4b | 0 (0) |
| - Grade 5 | 0 (0) |

*Highest grade of complication was used in patient who had more than one complication

only a few studies, that reported efficacies of carboplatin-based NAC. We found that our patients receiving GCb regimen had lower pCR (5.26%) and pPR rates (15.79%) compared to previously published studies[24-26], which revealed pCR and pPR rates ranging from 15-24.1% and 23.3-38%, respectively.[24-26] The difference could be caused by many reasons. Firstly, the proportion of locally advanced disease, including 72% of high T-stage (cT3-4), 22% of node involvement (cN+), and 8% of M1a disease, in our study was slightly higher than other published series. These might be the result of our early practice that most patients with organ-confined disease (cT2) tended to undergo immediate cystectomy rather than NAC prior to RC. Secondly, in this study, there was no specific criterion for determining who was cisplatin-unfit. In fact, renal insufficiency is a major issue that prevents many patients from receiving cisplatin therapy. However, considering our patients' mean creatinine clearance of 66.59 ml/min in the carboplatin group, it seemed that some of them would be better suited to cisplatin-based regimens. Thirdly, due to the small number of trials conducted so far, the response rates from previous studies that we compared may be a bit imprecise. Finally, we noticed that our patients in the carboplatin group had a slightly longer mean interval time from the last cycle of NAC to RC (47.4 days) when compared to the Murasawa et al trial[26] (< 30 days). However, the optimal time for RC following NAC that impacts NAC responsiveness is still unknown.

Recently, the literatures on predictive factors of NAC response in MIBC patients were thoroughly reviewed by European Association of Urology (EAU).[16] All aspects including disease-related factors, patient-related factors, and pathological factors were explored. Data from some literatures showed a significant association between pathologic response and specific parameters. For example, small series by Pokuri et al. demonstrated a positive correlation between pCR and the presence of pure urothelial carcinoma[31]; and Boeri at al. found that cigarette smoking was significantly associated with adverse pathological response to cisplatin-based NAC.[32] However, they finally concluded that there are currently no established tools in clinical practice for predicting pathologic

**Table 6.** Detail of perioperative complications

| Perioperative complications, no. (%) | Minor complication (Clavien-Dindo grade < 2) | Major complication (Clavien-Dindo grade > 3A) |
|---|---|---|
| Wound complications | 2 (2.7) | 1 (1.3) |
| Pulmonary complications | 2 (2.7) | 0 (0) |
| Renal insufficiency | 14 (18.7) | 0 (0) |
| Urinary leakage | 2 (2.7) | 0 (0) |
| Neurological complications | 3 (4) | 0 (0) |
| Anemia | 32 (42.7) | 1 (1.3) |
| Deep vein thrombosis | 0 (0) | 0 (0) |
| Infection | 4 (5.3) | 0 (0) |
| Prolong bowel ileus | 4 (5.3) | 0 (0) |
| Bowel injury | 4 (5.3) | 1 (1.3) |
| Gut obstruction | 1 (1.3) | 0 (0) |
| Lymphocele | 2 (2.7) | 2 (2.7) |

*Highest grade of complication was used in patient who had more than one complication

response to NAC. In our study, although, we discovered four parameters linked to pathologic downstaging in univariable analysis, there were only two after multivariable adjustment, which were Hb at first visit > 12 g/dl (OR 16.42, 95%CI 1.78-151.86, p = 0.01) and NLR < 3 (OR 12.81, 95%CI 1.36-120.9, p = 0.03).

NLR is the basic blood-based marker that has been thought to represent both systemic inflammation and antitumor immune response. An elevated NLR may indicate that the host is unable to develop a targeted immune response against tumor cells, and is related to a poor prognosis.[33] Our findings on the pre-neoadjuvant chemotherapy NLR were perfectly comparable to those from a larger retrospective study recently published by Black et al.[34] which showed that NLR > 3 was the only significant risk factor associated with a reduced response to NAC in multivariable analysis (OR 0.43, 95% CI 0.22-0.82, p = 0.01). Meanwhile, anemia and low hemoglobin (Hb) levels are highly typical in patients with malignant tumors. Furthermore, anemia has been linked to a poor outcome in a variety of malignancies.[35] According to a recent meta-analysis, preoperative anemia and low Hb levels in MIBC patients undergoing RC are significantly associated with earlier recurrence and even shorter survival.[36] Our study not only supports these findings but it's also the first one to show a correlation between Hb and pathologic response. Tumor hypoxia, which promotes tumor growth by stimulating angiogenesis and has been linked with resistance to chemotherapy, is one of the hypotheses that could explain this relevance.[35,36] Another interesting result from our study was that NAC regimens had no effect on the pathologic response, regardless of whether they were cisplatin-based or not (Table 2). This result may be caused by many limitations which are discussed later.

Although a few cohort studies reported the utility of GCb in its role as NAC prior to RC, the predicting factors for NAC response have yet to be thoroughly investigated. In our subgroup analysis focusing on GCb regimen, it appeared that tumor size smaller than 4 cm (OR 12, 95%CI 1.92-75.05, p = 0.008) was the only factor related to pathological response. Our median tumor size was 4.4 cm, which was comparable to the larger study from Murasawa et al (4.3 cm). According to the American Urological Association (AUA) guideline[37], tumor size is an essential determinant in the risk stratification to select subsequent management and a follow-up strategy in NMIBC. On the other hand, the usefulness of tumor size in MIBC was questionable. It's likely to be used only in bladder-sparing treatments such as trimodal therapy. We wish that our results could be adapted for use in MIBC patients who are cisplatin-ineligible, and that tumor size will be a promising predictive factor in the future for selecting patients who should be treated with chemotherapy before RC.

Earlier, Boonnam et al. has published a single-center retrospective study of perioperative outcomes in bladder cancer underwent RC at KCMH between 2003 and 2013.[38] Almost all of the 144 patients in their study underwent immediate RC except one patient who had NAC and three who received radiotherapy before RC. Their rates of major complications were slightly higher than ours (17.4% vs 10%). Operative outcome variables including median operative time, median estimated blood loss, and time to start soft diet from their study were 340 minutes, 1,700 ml, and 8 days, respectively. In comparison to our results, it appears to be superior to theirs. Despite the fact that the two trials differ in many aspects, we may presume that administering NAC before RC does not increase perioperative complications.

Our study has several limitations. The fact that it is a single-institution cohort with a retrospective design puts it at a high risk of bias. In addition, our study's sample size was relatively modest, and the population in our series with a high proportion of locally advanced disease, as described earlier, might not represent ideal candidates for NAC treatment prior to RC. Furthermore, many factors such as the patients' age, renal function, performance status, comorbidities, and oncologist's experience may all impact the decision to use the NAC regimen, which is solely determined by our oncologists. As a result, it appears that selection bias is unavoidable. Despite these limitations, the strength of our study is that we reported a real-world practice series that differed from the typically enrolled patients in the clinical trials. Moreover, it is worth noting that our series is one of a few published studies of carboplatin-base NAC in MIBC patients that have been reported so far.

## Conclusion

Pretreatment Hb and NLR were independently associated with pathologic response to NAC. For this reason, they have been determined as a prognostic marker in MIBC patient receiving NAC prior to RC. Furthermore, GCb followed by RC may be the standard treatment for MIBC patients who are unfit for cisplatin-based chemotherapy, particularly in those with tumors less than 4 cm in size. Finally, administering NAC prior to RC does not increase the risk of perioperative complications.

## Conflict of Interest

The authors declare no conflict of interest.

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