Running Head: Neoadjuvant carboplatin in locally advanced bladder cancer

Oncological Outcomes of Neoadjuvant Gemcitabine plus Carboplatin versus Gemcitabine plus Cisplatin in Locally Advanced Bladder Cancer: A Retrospective Analysis

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Abstract

Purpose: Cisplatin-based neoadjuvant chemotherapy (NAC) is the standard of care in non-metastatic muscle-invasive bladder cancer (MIBC). There are limited data regarding the alternative choices for cisplatin-ineligible patients. This study has investigated the oncological outcomes of gemcitabine plus cisplatin (Gem/Cis) and gemcitabine plus carboplatin (Gem/Carbo) in this setting.

Materials and Methods: One hundred forty consecutive patients with MIBC (cT2–T4a) receiving neoadjuvant Gem/Cis or Gem/Carbo before chemoradiation (CRT) or radical cystectomy (RC) were retrospectively evaluated between April 2009 and April 2019. Patients with ECOG performance status 2, creatinine clearance < 60 mL/min, hydronephrosis, ejection fraction < 50%, or single kidney received Gem/Carbo. The complete clinical response (cCR) and overall survival (OS) of NAC regimens were compared. Prognostic significance was assessed with Cox proportional hazards model.

Results: In total, 79 patients (56.4%) received Gem/Cis. The cCR was not significantly different between Gem/Cis and Gem/Carbo regimens (38.7% vs. 36.2%, $P = .771$). After NAC, 79 patients (56.4%) received CRT, and other cases underwent RC. After a median follow-up of 43 months, patients in the Gem/Cis group had significantly better OS than Gem/Carbo (median OS: 41.0 vs. 26.0 months, $P = .008$). Multivariable Cox proportional hazards models identified cT4a stage (95% confidence interval [95% CI]: 1.001–4.85, hazard ratio [HR] = 2.08, $P = .03$) and cCR (95% CI: 0.26–0.99, HR = 0.51, $P = .04$) as the only independent prognostic factors of OS, and ruled out the type of NAC regimen.

Conclusions: The choice of NAC (between Gem/Cis and Gem/Carbo) is not the predictor of survival and both regimens had similar cCR.

Keywords: Bladder cancer, Carboplatin, Cisplatin, Complete clinical response, Neoadjuvant chemotherapy, Overall survival, Prognostic factors

Introduction

Bladder cancer (BC) is the 12th most common malignancy and the 13th leading cause of cancer-related mortality worldwide.[1] Urothelial cell carcinoma (UCC) is the most frequent primary BC that accounts for 95% of cases, most of which are diagnosed at an early stage. This highlights the importance of locoregional therapy.[2]

For better management, BC is classified into three distinct categories: non-muscle invasive BC, muscle invasive BC (MIBC), and metastatic BC. Taking a step back, primary radical cystectomy (RC) was the standard treatment in MIBC. Investigators realized that distant metastasis was the main pattern of recurrence after RC.[3] Therefore, neoadjuvant chemotherapy (NAC) was proposed and dramatically improved the clinical outcomes of RC.[4] Alternative to RC, radiotherapy is an available choice—in case of complete response to NAC—to exclude the morbidity of surgery.[5] Currently, cisplatin-based neoadjuvant regimens such as gemcitabine plus cisplatin (Gem/Cis) and methotrexate, vinblastine, doxorubicin plus cisplatin (MVAC) are the standard regimens.[4] Despite these advantages, NAC is not widely employed in patients who are unfit for cisplatin-based NAC, including patients with Eastern Cooperative Oncology Group (ECOG) performance state of 2, single kidney, hydronephrosis, creatinine clearance (CrCl) < 60 mL/min, grade 2 of neuropathy, hearing loss, or cardiac failure class III (based on New York Heart Association classification).[6] Studies have demonstrated that 30–50% of the BC patients are ineligible for cisplatin.[7]

A carboplatin-based regimen could be a viable option for patients unfit for cisplatin. The use of carboplatin instead of cisplatin was investigated in other cancers such as malignant mesothelioma and lung cancers.[8-10] Currently, there is a paucity of convincing data supporting the use of carboplatin (as NAC) in MIBC patients who are ineligible for receiving cisplatin.[11] A few studies assigned a comparative response rate and survival;[12-15] however, a more recent retrospective cohort demonstrated superior pathologic response and survival in the cisplatin group.[16] This discrepancy might originate from selecting treatment regimens with totally different agents [i.e., MVAC (as the cisplatin-based regimen) vs. Gem/Carbo (as the carboplatin-based regimen)] in two studies [13,14] or unbalanced sample sizes in two other studies that could impact the power of the results.[12,16]

Considering these issues, this retrospective cohort was therefore designed to compare the clinical response and survival of a standard cisplatin-based NAC (Gem/Cis) and a carboplatin-based regimen (gemcitabine plus carboplatin [Gem/Carbo]) in MIBC.

Materials and Methods

The ethical approval was provided by the ethical committee of the XXX University of Medical Sciences (XXX.REC.1399.016).

Study Population

In this retrospective cohort study, the data from all consecutive patients with MIBC treated with Gem/Cis or Gem/Carbo as the NAC (before CRT or RC) from April 2009 to April 2019 at XXX were collected. The diagnosis of UCC was based on transurethral resection for bladder tumor (TURBT) results. Participants who had T2–T4aN0–1M0 (based on American Joint Committee on Cancer, 7th edition) urothelial carcinoma based on physical exam, TURBT, and computed tomography (CT) scan of chest, abdomen, and pelvis were enrolled. The cases recruited before January 1, 2010 (the release date of AJCC 7th edition) were re-evaluated for the possible changes in the T and N categories. Patients' data, including demographic features, clinical and pathologic characteristics, treatment schedules, and outcomes, were collected from medical records. The IRB of the XXX University of Medical Sciences approved the research. The IRB waived informed consent due to the retrospective nature of the study. The study was conducted per the principles of the Declaration of Helsinki and current ethical guidelines.

Treatment and Evaluation

Within four weeks after maximal TURBT, patients were permitted to receive NAC with four cycles of Gem/Cis (gemcitabine 1000 mg/m² on days 1 and 8 plus cisplatin 35 mg/m² on days 1 and 2, every 21 days) or Gem/Carbo regimen (gemcitabine 1000 mg/m² on days 1 and 8 plus carboplatin area under the curve [AUC] 4 on day 1, every 21 days). Patients with ECOG performance status 2, creatinine clearance < 60 mL/min (using Cockcroft-Gault equation [17]), hydronephrosis, ejection fraction < 50%, or single kidney received Gem/Carbo regimen. Patients with ECOG 0-1 were eligible for Gem/Cis, and those with ECOG 3-4 were not candidates for chemotherapy. During the administration of treatment, the daily dose of regimens could be adjusted according to the frequency and severity of adverse effects. Clinical response (ycTNM) was evaluated according to RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria using cystoscopic tumor-site biopsy, urine cytology, and restaging CT scan within four weeks. Thereafter patients with incomplete responses to NAC proceeded to immediate RC. Patients who were unfit for surgery, patients with a complete response to NAC, or those who were unwilling to undergo RC received CRT. CRT was carried out in 2 distinct approaches, 1) node-negative patients: whole bladder to a

total prescribed dose of 64 Gy, 2) node-positive patients: whole bladder + pelvic lymph nodes 45 Gy, then boost to the whole bladder to a total prescribed dose of 64 Gy. Radiotherapy was delivered five days per week at a 1.8 Gy daily dose. Cisplatin 15 mg/m^2 plus fluorouracil 400 mg/m^2 was administered during radiotherapy on days 1–3, 8–10, and 15–17. After chemoradiation, patients were re-evaluated with cystoscopy and chest, abdomen, and pelvic CT scans, and regular follow-up was performed for patients at 6-month intervals.

Endpoints

In this study, complete clinical response (cCR) and overall survival (OS) were evaluated as the primary and secondary objectives, respectively. The cCR was defined as negative results for cystoscopic tumor-site biopsy, urine cytology, and imaging (chest, abdomen, and pelvic CT scans) four weeks after NAC, and OS was defined as the time from the start of NAC until death from any cause. In addition, the association of covariates with cCR and the prognostic significance of them on the OS of patients were evaluated.

Statistical Analysis

Categorical variables were summarized as numbers and percentages and were compared using the Pearson chi-square test. Continuous variables were summarized using mean and standard deviation, and intergroup values were compared using the independent t-test. OS was calculated using the Kaplan–Meier method, and intergroup differences were compared with a log-rank test. Potential prognostic factors for OS were assessed with univariable and multivariable Cox proportional hazards models. All factors exhibiting significant association with OS in the univariable analyses were included in a multivariable model. The follow-up time was estimated using the reverse Kaplan-Meier method.[18] All analyses were performed using IBM SPSS Statistics, version 26. The statistical significance level was set to 0.05, except for including covariates into multivariable analysis that *P*-value was set to 0.20 to impede missing the possible potential predictive factors. [19]

Results

From April 2009 to April 2019, 140 patients with MIBC who received NAC before CRT or RC were enrolled in the study. Patients had a mean age of 66.3±10.4 years, and 130 cases (92.8%) were male. Compared to the Gem/Cis, patients in the Gem/Carbo group were older (mean age 61.4±9 vs. 72.8±8.4, $P < .001$). UCC was the only pathology diagnosis, which was high grade in

136 patients (97.2%). The tumor stage was clinical (c)T2 in 80 patients (57.1%), cT3 in 48 patients (34.3%), and cT4a in 11 patients (7.9%) (~~one patient was missed according to clinical stage subclassification~~the clinical staging of one patient was not available), and nodal status was negative in 102 patients (72.8%) without significant difference between groups (*P* > .05). In total, 79 (56.4%) and 61 (43.6%) patients received Gem/Cis and Gem/Carbo as NAC. The mean CrCl was 59.0 mL/min, which was significantly higher in the cisplatin group (69.9 vs. 44.8 mL/min, *P* = .003). Other baseline characteristics were comparable across the groups (Table 1). Overall, 128 patients (91.7%) received optimal chemotherapy cycles, which was not statistically different between Gem/Cis (93.6%, 74 cases) and Gem/Carbo (88.5%, 54 cases) groups (*P* = 0 .44). This subgroup did not differ significantly in baseline characteristics compared to the suboptimal group [optimal vs. suboptimal: male sex *P* = .32, T stage *P* = .53, N status *P* = .36, tumor grade *P* = .54, smoking status *P* = .69, and previous BCG therapy *P* = .60). After NAC, 79 patients (56.4%) received CRT and other cases underwent immediate RC (*P* = .90).

[Table 1 near hear]

Association Between Chemotherapy Regimen and Tumor Response

Of the study population, 50 cases (37.6%) attained cCR that was not significantly different between Gem/Cis and Gem/Carbo regimens (38.7 vs. 36.2%, *P* = .771). Likewise, the rate of cCR was not significantly associated with age (*P* = .51), ~~gender~~ sex (*P* = .99), tumor stage (*P* = .53), nodal involvement (*P* = .32), tumor grade (*P* = .99), and CrCl (*P* = .57). The detailed results of cCR based on covariates are presented in Table 2.

[Table 2 near hear]

Association Between Chemotherapy Regimen and Survival

Following a median follow-up of 43 months (95% confidence interval [95% CI]: 36.3–49.6 months), 71 patients (50.7%) ~~had~~ died. In total, the median OS of patients receiving NAC was 33 months (95% CI: 24.3–41.6 months), which was significantly longer in Gem/Cis group (median OS 41.0 months [95% CI: 37–44.9] vs. 26.0 months [95% CI: 17–35], *P* = .008) (Figure 1-A). Concerning patients who completed four cycles of NAC, the median OS was 33 months, including 40 months (95% CI: 32.3–47.6) and 26 months (95% CI: 17–34.9) for Gem/Cis and Gem/Carbo groups, respectively (*P* = .015).

Prognostic Factors of Survival

Univariable analysis of pre-treatment covariates revealed that NAC regimen (Gem/Carbo: 95% CI: 1.16–3.03, hazard ratio [HR] = 1.88, P = .01), CrCl (CrCl < 60 mL/min: 95% CI: 1.16–3.11, HR = 1.90, P = .01), age (> 65 years: 95% CI: 1.13–2.94, HR = 1.82, P = .01), and tumor stage (cT4a: 95% CI: 1.06–5.46, HR = 2.41, P = .03) were significantly associated with OS. Figure 1 illustrates the comparison of OS based on the significant pre- and post-treatment covariates. On multivariable analysis, presence of cT4a disease (95% CI: 1.001–4.85, HR = 2.08, P = .03) was identified as an independent risk factor for shorter OS. Of note, due to the significant correlation between nodal status and tumor stage (P < .0001), the nodal status was not included in the multivariable model.

[Figure 1 near hear]

In univariable analysis of post-treatment covariates, both cCR (95% CI: 0.26–0.80, HR = 0.45, P = .007) and the treatment following NAC (95% CI: 0.34–0.90, HR = 0.55, P = .01) were found to have significant association with OS. Multivariable analysis outlined cCR (95% CI: 0.26–0.99, HR = 0.51, P = .04) as the independent prognostic factor of OS (Table 3).

[Table 3 near hear]

Discussion

Level 1 evidence has demonstrated that cisplatin-based NAC (MVAC, Gem/Cis) has improved the OS of RC in MIBC.[4] The standard NAC regimen, however, has not been established for patients who are unfit for cisplatin that constitute 30–50% of BC patients.[4,7,20] Therefore, this study—among a few others (Table 4)—was conducted firstly to compare the clinical response and survival of a carboplatin-based (Gem/Carbo) NAC against the standard cisplatin-based regimen (Gem/Cis); secondly, to find the relevant prognostic factors ~~of these oncological outcomes.~~ .

[Table 4 near hear]

In summary, this study demonstrated comparable cCR between induction Gem/Cis and Gem/Carb in patients with MIBC. In addition, the multivariable analysis showed that the choice of NAC

between Gem/Cis and Gem/Carbo had no independent effect on OS. This might reside in the similar mode of action and pharmacodynamic between cisplatin and carboplatin; both platinum agents induce apoptosis through the formation of DNA adducts, and the intracellular concentration of both is regulated by a common influx (i.e., copper transporter CTR1) and efflux proteins (i.e., ATP7A-B).[21,22] The comparable results for cCR (Gem/Cis 38.7 vs. Gem/Carbo 36.2%, *P* = .77) is consistent with the Mertens *et al*. study.[14] This finding is also in line with the Iwasaki *et al*. and Schinzari *et al*. studies that reported comparable partial pathological response (pPR) to MVAC versus Gem/Carbo regimens (53 vs. 62%, *P* = .6) and complete pathological response (pCR) to Gem/Cis versus Gem/Carbo (36 vs. 23.8%, *P* = .35), respectively.[13,15] In the present study, in contrast to the Iwasaki *et al*. and Anan *et al*. studies, the median survival rates between cisplatin- and carboplatin-based NAC (41 vs. 26 months, P = .008) were not comparable.[13,23] This might root in the selection bias of this study that patients in the Gem/Carbo group were significantly older with lower CrCl (both with poorer prognosis). Peyton *et al.* demonstrated shorter 2-year OS in carboplatin-based regimen (34.8 [Gem/Carbo] vs. 73.3 [dose-dense MVAC (ddMVAC)], 62% [Gem/Cis], *P* = .002) that was confirmed in multivariable analysis (Gem/Cis [reference = 1], ddMVAC [95% CI: 0.17–1.06, HR = 0.42, *P* = .07], Gem/Carbo [95% CI: 1.16–3.44, HR = 2, *P* = .01]).[16] In the current study, however, the multivariable analysis did not confirm the preliminary results. This is explained in detail in the following paragraph. In summary, all the aforementioned studies except for one (Peyton *et al.* study) agree with the similar response (clinical, pathological) to NAC between carboplatin- and cisplatin-based regimens. On survival analysis, 43 ~~43~~ of 65 ~~65~~ studies showed comparable survival between study groups, and the other 2 (Peyton *et al.* and current studies) reported shorter OS in the carboplatin-based group that might be affected by selection bias.

On univariable analysis of pre-treatment covariates, predictors of worse OS were Gem/Carbo regimen, CrCl < 60 mL/min, age > 65 years, and T4 tumors. However, multivariable analysis ruled out the prognostic significance of the NAC regimen. It confirmed Peyton *et al.*'s findings, in which the advanced tumor stage was an independent predictor for the poor OS.[16] In the current study, OS was considerably longer than that reported by Mertens *et al*. (median OS 33 vs. 22 months) using similar chemotherapy regimens, which could be due in part to the lower proportion of patients with cT4 disease in this study (7.9 vs. 48.3%). This finding highlights the advanced tumor stage as an independent prognostic factor in this setting.[14] Univariable analysis of post-treatment

covariates put forward the cCR and CRT—against RC—as the prognostic factors of OS. However, multivariable analysis ruled out CRT that might originate from our approach, of which patients with cCR to NAC (with better prognosis) were proceeded to CRT and confirmed cCR as an independent prognostic factor of OS. This finding is consistent with the literature highlighting the pCR as the prognostic factor of disease-specific survival and OS. [14,15]

In this study, the complete response to NAC was not associated with variables such as age, sex, clinical tumor stage, and smoking history. So far, few other studies have intended to find predictive factors of response to NAC. In a large series, Zargar *et al*. stated that any downstaging of tumors (pPR and pCR) is reduced by nearly 40% in cT3–4 tumors.[24] Subsequently, Peyton *et al*. demonstrated that ddMVAC provides more downstaging of the tumor (vs. Gem/Cis: 95% CI: 1.10–3.09, odds ratio [OR] = 1.84, P = .02).[16] A more recent analysis showed that neutrophil-to-lymphocyte ratio (NLR) > 3 could predict decreased response to NAC; however, it did not demonstrate an association with age, sex, tumor stage, and smoking that confirms the findings of the present study.[25] Accordingly, over the last decade, investigators have tried to introduce predictive biomarkers (e.g., somatic ERCC2 mutation); however, none are yet validated for routine clinical use.[25,26]

Along with preceding comparative studies, several other retrospective studies have reported the clinical outcomes of carboplatin-based NAC in MIBC. Koie *et al*. (2015) showed a significant reduction in local (5.4 vs. 14.3%), regional (5.4 vs. 22.3%), and distant recurrence (3.8 vs. 20%) after neoadjuvant Gem/Carbo compared to RC alone. [27] Murasawa *et al*. reported improvement in 5-year OS (79.5 vs. 53.8%), 5-year disease-free survival (DFS) (75.5 vs. 55.4%), pCR (16.3%), and RC with negative surgical margins (100 vs. 87.7%) after neoadjuvant Gem/Carbo versus RC alone in cisplatin-ineligible MIBC patients ~~who are ineligible for cisplatin~~.[28] Likewise, Koie *et al*. (2014) demonstrated a significant improvement in 5-year OS and DFS with neoadjuvant Gem/Carbo before RC (98.6 vs. 66.6% and 94.2 vs. 72.7% respectively) in patients with cT2 bladder cancer.[29] Overall, these findings might address the feasibility of neoadjuvant carboplatin-based chemotherapy for patients who are ineligible for cisplatin.

The limitations of the present study need to be considered, including its retrospective design, no randomization, variable post NAC treatments. Due to its retrospective nature, selection and information bias cannot be totally excluded. The bias effect of uncontrolled confounding factors is required to be acknowledged as well. The NAC dose density, treatment delay, dose adjustment,

or safety were not included in the analysis. In addition, using clinical response as a primary endpoint, a proportion of patients who had a persistent disease in RC specimen were ignored. Also, the short follow-up for the survival data and failure to report the other oncological endpoints (e.g., DSS, DFS) are acknowledged. Despite these limitations, this is one of the largest series comparing the oncological outcomes of a ~~gemcitabine~~carboplatin-based NAC with a standard cisplatin-based regimen in MIBC. Moreover, the study groups of the current study are more balanced in sample size (in comparison with Peyton *et al*. and Anan *et al*. studies) that could enhance the power of the results.

Conclusions

This study showed that the choice of NAC between Gem/Carbo and Gem/Cis in MIBC has no impact on cCR and OS. Also, it suggested that advanced tumor stage and cCR are two independent prognostic factors in this setting. Hence, Gem/Carbo seems to be an appropriate option for patients with MIBC who are unfit for cisplatin to enable them to benefit from NAC advantages. Randomized comparative trials are required to delineate the efficacy of neoadjuvant carboplatin-based regimens definitively.

Author's contribution: All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, B.M.; Methodology, A.R. and F.T.H.; Investigation, A.J., M.G, and F.T.H.; Formal Analysis, A.R. and F.T.H.; Resources, B.M, A.B., and MR.F..; Writing - Original Draft, A.J. and F.T.H.; Writing - Review & Editing, F.T.H. and A.R.; Visualization, MR.F..; Supervision, B.M. and M.H.

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References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin.n/a.
2. Al-Husseini MJ, Kunbaz A, Saad AM, et al. Trends in the incidence and mortality of transitional cell carcinoma of the bladder for the last four decades in the USA: a SEER-based analysis. BMC Cancer. 2019;19:46.
3. Li G, Niu H-m, Wu H-t, et al. Effect of cisplatin-based neoadjuvant chemotherapy on survival in patients with bladder cancer: a meta-analysis. Clinical and Investigative Medicine. 2017E81-E94.
4. Hamid ARAH, Ridwan FR, Parikesit D, Widia F, Mochtar CA, Umbas R. Meta-analysis of neoadjuvant chemotherapy compared to radical cystectomy alone in improving overall survival of muscle-invasive bladder cancer patients. BMC Urol. 2020;20:158.
5. Mirza A, Choudhury A. Bladder preservation for muscle invasive bladder cancer. Bladder Cancer. 2016;2:151-63.
6. Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. The lancet oncology. 2011;12:211-4.
7. Einstein DJ, Sonpavde G. Treatment approaches for cisplatin-ineligible patients with invasive bladder cancer. Curr Treat Options Oncol. 2019;20:1-13.
8. Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma: results of the International Expanded Access Program. J Thorac Oncol. 2008;3:756-63.
9. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin-or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. 2012.
10. Vasconcellos VF, Marta GN, da Silva EM, Gois AF, de Castria TB, Riera R. Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer. Cochrane Database Syst Rev. 2020.
11. Ho GY, Woodward N, Coward JI. Cisplatin versus carboplatin: comparative review of therapeutic management in solid malignancies. Crit Rev Oncol Hematol. 2016;102:37-46.
12. Anan G, Hatakeyama S, Fujita N, et al. Trends in neoadjuvant chemotherapy use and oncological outcomes for muscle-invasive bladder cancer in Japan: a multicenter study. Oncotarget. 2017;8:86130.
13. Iwasaki K, Obara W, Kato Y, Takata R, Tanji S, Fujioka T. Neoadjuvant gemcitabine plus carboplatin for locally advanced bladder cancer. Jpn J Clin Oncol. 2013;43:193-9.
14. Mertens LS, Meijer RP, Kerst JM, et al. Carboplatin based induction chemotherapy for nonorgan confined bladder cancer—a reasonable alternative for cisplatin unfit patients? The Journal of urology. 2012;188:1108-14.
15. Schinzari G, Monterisi S, Pierconti F, et al. Neoadjuvant chemotherapy for patients with muscle-invasive urothelial bladder cancer candidates for curative surgery: A prospective clinical trial based on cisplatin feasibility. Anticancer Res. 2017;37:6453-8.
16. Peyton CC, Tang D, Reich RR, et al. Downstaging and Survival Outcomes Associated With Neoadjuvant Chemotherapy Regimens Among Patients Treated With Cystectomy for Muscle-Invasive Bladder Cancer. JAMA Oncol. 2018;4:1535-42.
17. Cockcroft DW, Gault H. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.
18. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;17:343-6.
19. Schwender H. David W. Hosmer, Stanley Lemeshow, Susanne May: Applied survival analysis: regression modeling of time-to-event data: Springer Nature BV; 2012.

20. Koshkin VS, Barata PC, Rybicki LA, et al. Feasibility of Cisplatin-Based Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer Patients With Diminished Renal Function. Clin Genitourin Cancer. 2018;16:e879-e92.
21. Sousa GFd, Wlodarczyk SR, Monteiro G. Carboplatin: molecular mechanisms of action associated with chemoresistance. Brazilian Journal of Pharmaceutical Sciences. 2014;50:693-701.
22. Li T, Peng J, Zeng F, et al. Association between polymorphisms in CTR1, CTR2, ATP7A, and ATP7B and platinum resistance in epithelial ovarian cancer. Int J Clin Pharmacol Ther. 2017;55:774-80.
23. Anan G, Hatakeyama S, Fujita N, et al. Trends in neoadjuvant chemotherapy use and oncological outcomes for muscle-invasive bladder cancer in Japan: a multicenter study. Oncotarget. 2017;8:86130-42.
24. Zargar H, Espiritu PN, Fairey AS, et al. Multicenter assessment of neoadjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2015;67:241-9.
25. Black AJ, Zargar H, Zargar-Shoshtari K, et al. The prognostic value of the neutrophil-to-lymphocyte ratio in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy and radical cystectomy. Paper presented at: Urologic Oncology: Seminars and Original Investigations, 2020.
26. Van Allen EM, Mouw KW, Kim P, et al. Somatic ERCC2 mutations correlate with cisplatin sensitivity in muscle-invasive urothelial carcinoma. Cancer Discov. 2014;4:1140-53.
27. Koie T, Ohyama C, Yamamoto H, et al. Differences in the recurrence pattern after neoadjuvant chemotherapy compared to surgery alone in patients with muscle-invasive bladder cancer. Med Oncol. 2015;32:421.
28. Murasawa H, Koie T, Ohyama C, et al. The utility of neoadjuvant gemcitabine plus carboplatin followed by immediate radical cystectomy in patients with muscle-invasive bladder cancer who are ineligible for cisplatin-based chemotherapy. Int J Clin Oncol. 2017;22:159-65.
29. Koie T, Ohyama C, Yamamoto H, et al. Neoadjuvant gemcitabine and carboplatin followed by immediate cystectomy may be associated with a survival benefit in patients with clinical T2 bladder cancer. Med Oncol. 2014;31:949.

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Table 1. Baseline characteristics and treatment types of the study population

Characteristics	**Total (N = 140)**	**Gem/Cis (N = 79)**	**Gem/Carbo (N = 61)**	***P*-value**

Age,				**< .001**
Mean (SD), years	66.3 (10.4)	61.4 (9.0)	72.8 (8.4)	
Sex, N (%)				.813
Female	10 (7.1)	6 (7.6)	4 (6.6)	
Male	130 (92.8)	73 (92.4)	57 (93.4)	
Tumor stage, N (%)				.360
T2	80 (57.1)	47 (59.5)	33 (54.1)	
T3	48 (34.3)	28 (35.4)	20 (32.8)	
T4a	11 (7.9)	4 (5.1)	7 (11.5)	
Missing	1 (0.7)	0	1 (1.6)	
Nodal status, N (%)				.831
Negative	102 (72.8)	57 (72.2)	45 (73.8)	
Positive	38 (27.2)	22 (27.8)	16 (26.2)	
Tumor grade, N (%)				.279
Low	4 (2.8)	4 (5.1)	0	
High	136 (97.2)	75 (94.9)	61 (100)	
Creatinine clearance,				**.003**
Mean (SD), mL/min	59.0 (20.5)	69.9 (18.6)	44.8 (12.9)	
Previous BCG therapy, N (%)				.129
No	106 (75.7)	56 (70.9)	50 (82.0)	
Yes	34 (24.3)	23 (29.1)	11 (18.0)	
Smoking status, N (%)				.611
No	81 (57.8)	44 (55.7)	37 (60.6)	
Yes	59 (42.2)	35 (44.3)	24 (39.4)	
Following treatment, N (%)				.510
Radical cystectomy	61 (43.6)	34 (43.1)	27 (44.3)	
Chemoradiotherapy	79 (56.4)	45 (56.9)	34 (55.7)	

Abbreviations: BCG, bacillus Calmette Guerin; Gem/Carbo, gemcitabine plus carboplatin; Gem/Cis, gemcitabine plus cisplatin; SD, standard deviation.

Table 2. Association of covariates with the clinical complete response to chemotherapy

Covariates	Without complete response (N = 83)	With complete response (N = 50)	*P*-value
Age, N (%)			.516
≤ 65 yr	43 (65.1)	23 (34.9)	
> 65 yr	40 (59.7)	27 (40.3)	
Sex N (%)			.999
Female	6 (60.0)	4 (40.0)	
Male	77 (62.6)	46 (37.4)	
Tumor stage, N (%)			.536
T2	45 (58.4)	32 (41.6)	
T3	31 (67.4)	15 (32.6)	
T4a	7 (70.0)	3 (30.0)	
Nodal status, N (%)			.320
Negative	63 (64.9)	34 (35.1)	
Positive	20 (55.5)	16 (44.6)	
Tumor grade, N (%)			.999
High	81 (62.3)	49 (37.7)	
Low	2 (66.7)	1 (33.3)	
Chemotherapy regimen, N (%)			.771
Gem/Cis	46 (61.3)	29 (38.7)	
Gem/Carbo	37 (63.8)	21 (36.2)	
Creatinine clearance, N (%)			.570
≥ 60 mL/min	34 (59.6)	23 (40.4)	
< 60 mL/min	49 (64.4)	27 (35.6)	
Previous BCG therapy, N (%)			.806
Yes	63 (63.0)	37 (37.0)	
No	20 (60.6)	13 (39.4)	
Smoking status, N (%)			.906
No	49 (64.5)	27 (35.5)	
Yes	34 (61.8)	21 (38.2)	

Abbreviations: BCG, bacillus Calmette Guerin; Gem/Carbo, gemcitabine plus carboplatin; Gem/Cis, gemcitabine plus cisplatin.

Table 3. Univariable and multivariable analysis of factors related to overall survival

Covariates	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
	Univariable analysis		Multivariable analysis [a]	
Pre-treatment covariates				
NAC regimen,				
Gem/Cis	1 (reference)		1 (reference)	
Gem/Carbo	1.88 (1.16-3.03)	**.010**	1.28 (0.70-2.36)	.402
Creatinine clearance,				
≥ 60 mL/min	1 (reference)		1 (reference)	
< 60 mL/min	1.90 (1.16-3.11)	**.011**	1.34 (0.71-2.52)	.333
Age,				
≤ 65 yr	1 (reference)		1 (reference)	
> 65 yr	1.82 (1.13-2.94)	**.014**	1.47 (0.84-2.57)	.161
Tumor stage,				
T2	1 (reference)		1 (reference)	
T3	1.08 (0.65-1.78)	.766	0.97 (0.58-1.63)	.905
T4a	2.41 (1.06-5.46)	**.034**	2.08 (1.001-4.85)	**.033**
Nodal status,				
Negative	1 (reference)			
Positive	1.52 (0.93-2.50)	.095		
Tumor grade,				
High	1 (reference)			
Low	2.89 (0.39-21.54)	.300		
Gender,				
Female	1 (reference)			
Male	1.36 (0.49-3.75)	.545		
Smoking status,				
No	1 (reference)			
Yes	1.08 (0.67-1.72)	.741		
Previous BCG therapy,				
Yes	1 (reference)			
No	1.05 (0.62-1.80)	.836		
Post-treatment covariates				
cCR				
No	1 (reference)		1 (reference)	
Yes	0.45 (0.26-0.80)	**.007**	0.51 (0.26-0.99)	**.041**
Following treatment				
Radical cystectomy	1 (reference)		1 (reference)	
Chemoradiotherapy	0.55 (0.34-0.90)	**.018**	0.78 (044-1.38)	.399

Abbreviations: BCG, bacillus Calmette Guerin; cCR, complete clinical response; Gem/Carbo, gemcitabine plus carboplatin; Gem/Cis, gemcitabine plus cisplatin; NAC, neoadjuvant chemotherapy.

[a] Chemotherapy regimen, creatinine clearance, age, and tumor stage were included in the pre-treatment multivariable model. Besides, clinical complete response and following treatment were included in the post-treatment model.

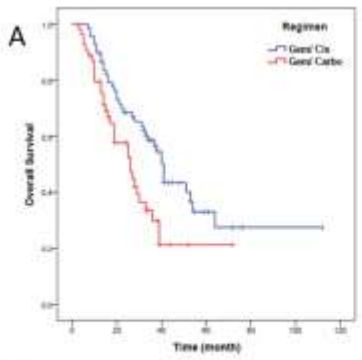
Table 4. Characteristics of studies comparing clinical outcomes of a neoadjuvant carboplatin-based regimen with standard cisplatin-based regimen

Studies	Type	Number of patients		NAC regimen		Treatment	Outcomes			*P*-value
		Cis	Carbo	Cis	Carbo			Cis	Carbo	
Mertens *et al*. (2012)	Retrospective cohort	83	23	Gem/Cis MVAC	Gem/Carbo	NAC + RC	cCR (%)	33.7	26.7	.65
							Median DSS (m)	20	18	.18
							Median OS (m)	22	22	.36
Iwasaki *et al*. (2013)	Retrospective cohort	34	34	MVAC	Gem/Carbo	NAC + RC	pPR (%)	62	53	.62
							3-years RFS (%)	79	75	.85
Schinzari *et al*. (2017)	Clinical trial (phase II)	30	42	Gem/Cis	Gem/Carbo	NAC + RC	pCR (%)	36	23.8	.35
							Median DFS [a] (m)	40	22	.57
							Median OS [a] (m)	48	> 50	.89
Anan *et al*. (2017)	Retrospective cohort	43	280	Gem/Cis	Gem/Carbo	NAC + RC	pCR (%)	5.7	17	NR
							5-year PFS [a] (%)	78	70	.32
							5-year OS [a] (%)	72	70	.24
Peyton *et al*. (2018)	Retrospective cohort	250	32	ddMVAC Gem/Cis	Gem/Carbo	NAC + RC	pPR	52 (ddMVAC) 41.3 (Gem/Cis)	27	**.03**
							pCR	41.3 (ddMVAC) 24.5 (Gem/Cis)	9.4	.05
							2-year OS (%)	73.3 (ddMVAC) 62 (Gem/Cis)	34.8	**.002**
Current study (2021)	Retrospective cohort	79	61	Gem/Cis	Gem/Carbo	NAC + RC NAC + CRT	cCR (%)	38.7	36.2	.77
							Median OS (m)	41	26	**.008**

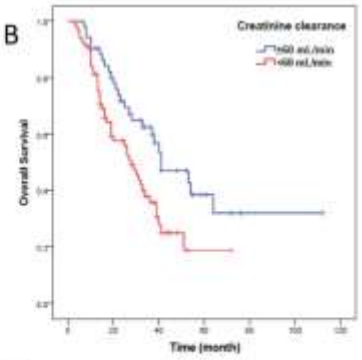
Abbreviations: Carbo, carboplatin-based; cCR, complete clinical response; Cis, cisplatin-based; CRT, chemoradiation; ddMVAC, dose-dense MVAC; DFS, disease-free survival; DSS, disease-specific survival; Gem/Carbo, gemcitabine plus carboplatin; Gem/Cis, gemcitabine plus cisplatin; MVAC, methotrexate, vinblastine, doxorubicin plus cisplatin; NAC, neoadjuvant chemotherapy; NR, not reported; OS, overall survival; pCR, complete pathological response; PFS, progression-free survival; pPR, partial pathological response; RC, radical cystectomy; RFS, relapse-free survival.

[a] Estimated based on the Kaplan-Meier curves

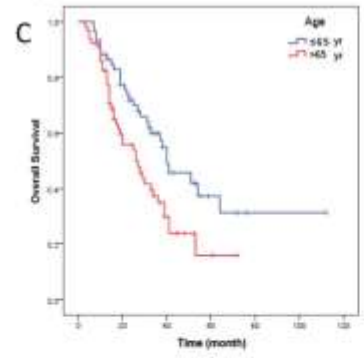
Figure 1. Kaplan-Meier curves of overall survival based on the significant pre-treatment factors, A) NAC regimen, B) creatinine clearance, C) age, and D) tumor stage, and post-treatment factors, E) complete clinical response, F) post-neoadjuvant treatment.



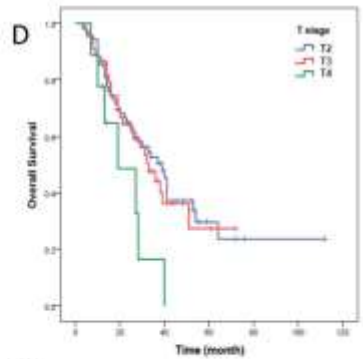
No. at risk						
Gem/Cis	67	43.5	19.5	4.5	1	0.5
Gem/Carbo	49	19.5	2.5	0.5		



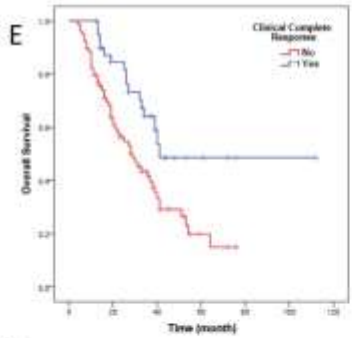
No. at risk						
CrCl ≥ 60 mL/min	50	32.5	14.5	4.5	1	0.5
CrCl < 60 mL/min	66	30.5	7.5	0.5		



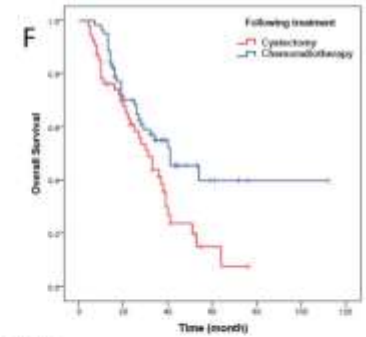
No. at risk						
≤ 65 years	57	35.5	14.5	4	1	0.5
> 65 years	59	27.5	7.5	1		



No. at risk						
T2	66	36.5	14.5	3.5	1	0.5
T3	42	23.5	6.5	1.5		
T4	8	3	1			



No. at risk						
With cCR	99.5	55.5	17.5	4.5	1	0.5
Without cCR	10.5	4	2.5			



No. at risk						
CRT	59	33	13.5	3.5	1	0.5
RC	44	27.5	7	1		

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