Original Article

Significance of split-dose cisplatin-based neoadjuvant chemotherapy followed by robotic-assisted radical cystectomy for muscle invasive bladder cancer

Keita Nakane^, Ayaka Okamoto, Hiroki Kato, Hiroki Hoshino, Teppei Nishiwaki, Torai Enomoto, Masayuki Tomioka, Tomoki Taniguchi, Makoto Kawase, Kota Kawase, Daiki Kato, Koji Iinuma, Yuki Tobisawa^, Takuya Koie^

Department of Urology, Gifu University Graduate School of Medicine, Gifu, Japan

Contributions: (I) Conception and design: K Nakane, T Koie; (II) Administrative support: A Okamoto, H Kato; (III) Provision of study materials or patients: K Nakane, H Kato, T Nishiwaki, T Enomoto, T Taniguchi, M Kawase, K Kawase, D Kato, K Iinuma; (IV) Collection and assembly of data: K Nakane, Y Tobisawa; (V) Data analysis and interpretation: K Nakane, T Koie; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Takuya Koie, MD, PhD. Department of Urology, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan. Email: koie.takuya.h2@f.gifu-u.ac.jp.

Background: Although cisplatin is essential for neoadjuvant chemotherapy (NAC) in patients with muscle-invasive bladder cancer (MIBC), good renal function is a prerequisite for those patients receiving NAC. However, patients with normal renal function may experience nephrotoxicity after cisplatin administration. We investigated the safety and efficacy of a split-dose regimen of gemcitabine and cisplatin (split-dose GC) in MIBC patients with normal renal function.

Methods: This retrospective study included 45 patients with MIBC who received standard GC, split-dose GC, or gemcitabine and carboplatin (GCarbo) as a NAC and subsequently underwent robot-assisted radical cystectomy. The efficacy and safety of two cycles split-dose GC were compared with those of other regimens.

Results: Among the 45 patients with MIBC, 14 received standard GC, 14 received split-dose GC, and 17 received GCarbo. Pathological complete response rates were 28.6%, 21.4%, and 29.4% for surgical specimens obtained post-treatment with standard GC, split-dose GC, and GCarbo, respectively (P=0.86). Renal function after NAC was significantly lower in the standard- and split-dose GC groups than in the GCarbo group (P<0.001).

Conclusions: Although the split-dose GC regimen showed a significant reduction compared to pre-treatment renal function, the pathological response rate and incidence of adverse events were similar to those of the other two regimens.

Keywords: Muscle-invasive bladder cancer (MIBC); neoadjuvant chemotherapy (NAC); cisplatin; cisplatin split-dose regimen; robot-assisted radical cystectomy (RARC)

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^ ORCID: Keita Nakane, 0000-0002-2589-1722; Yuki Tobisawa, 0000-0001-8026-9541; Takuya Koie, 0000-0002-2980-127X.

Introduction

Bladder cancer (BCa) is the ninth most common cancer (3.1%) among all malignancies, with 613,791 new cases diagnosed annually worldwide (1). Although radical cystectomy (RC) is the recommended standard of care for muscle-invasive bladder cancer (MIBC), improvements in oncological outcomes with RC alone have been limited (2-4). Previously, the combination of perioperative radiation therapy or chemotherapy with RC was employed to improve the outcome of MIBC (5,6). With regards to chemotherapy, the efficacies of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) have been demonstrated in locally advanced or metastatic BCa (7). Grossman *et al.* (8) conducted a randomized controlled trial (RCT) comparing the oncological outcomes in patients with MIBC treated with either a combination of neoadjuvant chemotherapy (NAC) using MVAC followed by RC or RC alone. The results showed that patients who underwent NAC had significantly improved overall survival (OS) rates, with the benefit being particularly pronounced in patients with a pathological complete response (pCR) (8). An RCT comparing the therapeutic efficacy of gemcitabine and cisplatin (GC) with MVAC as systemic chemotherapy for locally advanced or metastatic BC showed that GC was associated with comparable oncological outcomes and fewer adverse events (AEs) than MVAC (9). Since the results of this RCT were reported, GC has been adopted as the first-line NAC regimen for MIBC, demonstrating similar anti-tumor efficacy and fewer AEs compared to MVAC (10-12). A recent multicenter, randomized GETUG-AFU V05 VESPER trial compared the oncologic outcomes between dose-dense MVAC (dd-MVAC), with a high relative dose intensity, and GC for NAC (13). Although there was a trend toward lower progression-free survival rates (P=0.06), patients receiving dd-MVAC had significantly higher antitumor efficacy and a significantly longer time to recurrence than those receiving GC (P=0.001 and P=0.01, respectively) (13). Therefore, various guidelines recommend a cisplatin-based NAC, followed by RC, as the standard of care for MIBC (2,3,14).

Although cisplatin plays a pivotal role as a NAC for patients with MIBC, it is important to note that the administration of cisplatin requires good renal function and may lead to a future decline in renal function (15,16). Thus, although the National Comprehensive Cancer Network guidelines recommend a daily dose of 70 mg/m^2 of cisplatin for patients with MIBC who have normal renal function, 35 mg/m^2 of cisplatin in divided doses over 2 days is recommended for patients with MIBC who have impaired renal function (2). A study of the efficacy of different cisplatin dosing schedules reported that cisplatin split-dose groups tended to have a lower pCR than the normal dose group; however, no significant differences were observed (17). Although several retrospective studies have demonstrated the benefit of NAC with carboplatin (18-20), various guidelines do not recommend the use of carboplatin as an NAC due to its lower antitumor efficacy than cisplatin and the results of RCTs on metastatic BCs (2,3,14,21-24). We have administered split-dose GC as a NAC followed by robotic-assisted radical cystectomy (RARC) for patients with MIBC who have normal renal function since 2021.

In this study, we evaluated the efficacy and safety of split-dose GC compared to those of patients who received standard GC, as well as those of patients with MIBC and impaired renal function who received gemcitabine and carboplatin therapy as a NAC (GCarbo group). We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-2024-662/rc).

Highlight box

Key findings

- We retrospectively evaluated the efficacy of standard gemcitabine and cisplatin (GC) therapy and split-dose GC therapy as neoadjuvant chemotherapy (NAC) in patients with muscle-invasive bladder cancer (MIBC) with normal renal function. There was no significant difference in efficacy or deterioration of renal function after NAC between the two groups.

What is known and what is new?

- Split-dose GC therapy is regarded as a beneficial approach for patients with MIBC who have impaired renal function. However, the efficacy of split-dose GC therapy for patients with MIBC who have normal renal function, as well as the impact of this therapy on renal function, remains unclear.
- This study compared split-dose GC therapy with standard GC therapy in patients with normal renal function.

What is the implication, and what should change now?

- The findings of this study indicate that there is no significant difference in efficacy between standard GC therapy and split-dose GC therapy. Additionally, the decline in renal function with NAC is comparable between the two treatment groups. Therefore, it is reasonable to utilize standard GC therapy for patients with normal renal function.

Methods

Endpoints

The primary endpoint of this study was the efficacy and safety of each NAC regimen. The secondary endpoints were OS and recurrence-free survival (RFS) for each NAC regimen.

Patients

This retrospective single-center cohort study included patients with clinical T2–4 and clinical N0 MIBC who underwent RARC after NAC with standard GC, split-dose GC, and GCarbo at Gifu University Hospital between November 2018 and May 2023. Patients for whom the determination of treatment response after NAC was impossible due to tumor removal by transurethral surgery, those who changed their NAC regimen owing to renal function status, those with missing data, and those with adenocarcinoma and small cell carcinoma components, including sarcomatoid subtype in the pathological diagnosis, were excluded from the study.

Patient characteristics, including age, sex, height, weight, body mass index, and Eastern Cooperative Oncology Group performance status (ECOG-PS) (25), were extracted from medical interviews and physical examinations. Clinical T and N stages were diagnosed using the American Joint Committee on Cancer Staging Manual, 8th edition (26), based on information from computed tomography (CT) of the chest to the pelvic region and magnetic resonance imaging (MRI) of the bladder. The severity of treatment-related AEs, such as anemia, neutropenia, thrombocytopenia, and ototoxicity, were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (27). We investigated the following NAC-related factors: duration of NAC administration, time from the end of NAC to RARC, number of cases in which NAC could not be administered according to the established schedule, number of cases in which a reduced dose of anticancer drug was administered, and the best overall response (BOR) of NAC. Regarding renal function, the estimated glomerular filtration rate (eGFR) was measured before and after NAC administration and at three and six months after RARC. Perioperative outcomes were evaluated in terms of total operative time which was defined as the time taken from skin incision to completion of skin closure, estimated blood loss, intraoperative complications, length of postoperative hospital stay, and postoperative complications within 90 days after the RARC. Pathologic evaluation included examination of the resected specimen margin status, pCR rate, and pathologic downstaging (pDS) rate, defined as ≤ ypT1.

Treatment schedule of NAC

In all the groups, gemcitabine was administered at a dose of 1,000 mg/m^2 on days one and eight of the NAC. Cisplatin was administered at 70 mg/m^2 on day two in the standard GC group, and 35 mg/m^2 on days one and eight in the split-dose GC group. In the GCarbo group, carboplatin was administered on day two, with a target area under the free carboplatin plasma concentration versus time curve of 5 (28). All regimens consisted of one course lasting three weeks, and all the patients received two courses of NAC prior to RARC. If a blood test on the day before or the day of the scheduled NAC procedure exhibited a white blood cell count of grade ≥3 or platelet count of grade ≥2 based on the CTCAE 5.0, the dose of anticancer drug was reduced or discontinued.

Patient evaluation

At the end of two cycles of NAC administration, a CT of the chest to the pelvic region and an MRI of the bladder were performed to determine the therapeutic effect of NAC on the tumor. BOR after NAC administration was assessed using the Response Evaluation Criteria in Solid Tumors guide-lines version 1.1 and diagnosed as complete response (CR), partial response (PR), stable disease (SD), or disease progression (29).

Statistical analysis

The primary endpoint of this study was the efficacy and safety of each NAC regimen. The secondary endpoints were OS and recurrence-free survival (RFS) for each NAC regimen. All statistical analyses were performed using Easy R (EZR) version 1.56 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (30), a graphical user interface of R version 3.3.0 (The R Foundation for Statistical Computing, Vienna, Austria) (29). The OS was defined as the time from RARC to death, and RFS was defined as the time from RARC to distant metastasis, local recurrence, or death. Oncological outcomes were assessed using the Kaplan-Meier method, and differences in clinical variables were evaluated using the log-rank test. Continuous

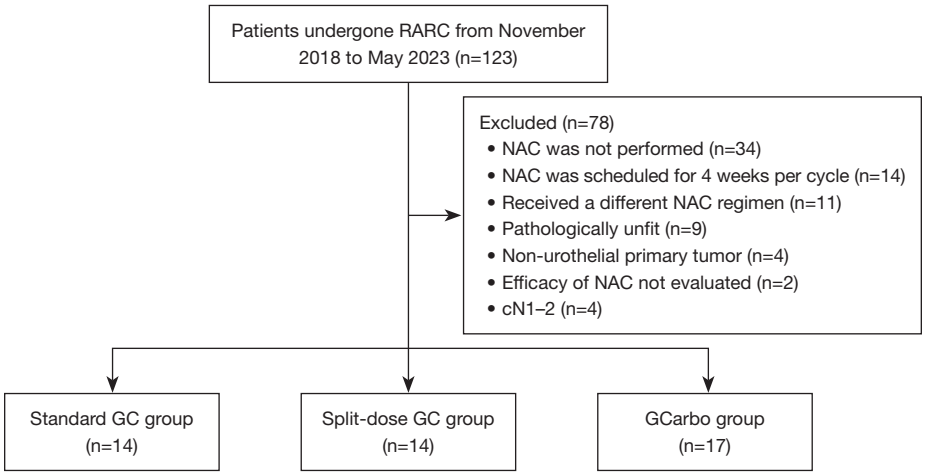

Figure 1 The flow diagram. NAC, neoadjuvant chemotherapy; GC, gemcitabine and cisplatin; GCarbo, gemcitabine and carboplatin; RARC, robotic-assisted radical cystectomy.

variables were analyzed using the Kruskal-Wallis test, categorical variables were analyzed using Fisher's exact test, and the Friedman test was used to analyze the change in eGFR in each NAC regimen group. For all analyses, a two-sided P value <0.05 was considered statistically significant.

Ethical statements

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Review Board of Gifu University Graduate School of Medicine (No. 2018-154, Dec 11, 2023). Informed consent was not obtained from each eligible patient, which was substituted with an opt-out option owing to the retrospective nature of this study. Based on the Japanese Ethics Committee and ethical guidelines, retrospective and cohort studies using existing literature and other sources stipulate that written consent is not required because the research information is publicly available. Details of this retrospective cohort study can be accessed, albeit only in Japanese, at https://rinri.med.gifu-u.ac.jp/esct/publish_document.aspx?ID=1049 (accessed Oct 11, 2024).

Results

Patient characteristics

During the enrollment period, 123 patients, including 4 patients with tumors not primary to the urothelium and 34 who did not undergo NAC, underwent RARC at our institution. Four patients with cN1–2, 9 patients who were pathologically unfit, 14 who received one course of NAC for four weeks, 11 who received a different NAC regimen for each course, and 2 for whom NAC efficacy could not be determined were ineligible. Finally, 45 patients were enrolled: 14, 14, and 17 in the standard GC, split-dose GC, and GCarbo groups, respectively (*Figure 1*).

Characteristics of the enrolled patients, clinical stages, and NAC-related parameters are shown in *Table 1*. The median age of patients at the time of RARC was 73 years [interquartile range (IQR), 68–78 years]; 71% of the patients were males, and the median follow-up period was 18.0 months (IQR, 4.0–32.0 months). The baseline eGFR was 62.1, 65.4, and 43.4 mL/min/1.73 m^2 in the standard GC, split-dose GC, and GCarbo groups, respectively (P<0.001). The median duration of NAC was 42 days (IQR, 42–47 days), and the median time from completion of NAC to RARC was 34 days (IQR, 24–41 days) for all treatment groups. BOR after NAC was 8.9% for CR, 26.7% for PR, 60.0% for SD, and 4.4% for PD. In total, 13.3% of all the patients skipped the chemotherapy schedule due to AEs, and 17.8% required a dose reduction of the NAC for the second cycle.

Surgical outcomes and perioperative complications are shown in *Table 2*. The median total operative time was 398 min (IQR, 296–457 min), the median operative time required for RARC was 112 min (IQR, 102–129 min), and median estimated blood loss was 180 mL (IQR, 100–320 mL). Overall, 3 (6.7%) patients required blood transfusions, and 1 (2.2%) had intraoperative complications. The

Table 1 Characteristics of the enrolled patients, their clinical stage, and NAC-related parameters

Covariates	Standard GC (n=14)	Split-dose GC (n=14)	GCarbo (n=17)	P value
Age (years)	72 [68–76]	67.5 [66–77]	75 [71–78]	0.14
Sex				0.69
Male	11 (78.6)	10 (71.4)	11 (64.7)	
Female	3 (21.4)	4 (28.6)	6 (35.3)	
ECOG-PS				0.34
0	10 (71.4)	9 (64.3)	8 (47.1)	
1	4 (28.6)	5 (35.7)	7 (41.2)	
2	0	0	2 (11.8)	
BMI (kg/m^2)	21.3 [19.7–22.7]	23.5 [19.9–24.7]	23.3 [21.2–26.3]	0.43
eGFR before NAC (mL/min/1.73 m^2)	62.1 [59.9–77.8]	65.4 [54.1–71.0]	43.4 [38.1–51.2]	<0.001
Follow-up period (months)	22.5 [20.0–26.0]	20 [19.0–21.7]	23 [18.0–26.0]	0.38
Pathology				0.22
Pure UC	12 (85.7)	12 (85.7)	14 (82.4)	
UC with squamous cell differentiation	0	2 (14.3)	2 (11.8)	
UC with glandular differentiation	2 (14.3)	0	1 (5.9)	
Clinical T				0.65
T2	9 (64.2)	10 (71.4)	11 (64.7)	
T3	3 (21.4)	4 (28.6)	3 (17.6)	
T4a	2 (14.3)	0	3 (17.6)	
Clinical N				>0.99
N0	14 (100.0)	14 (100.0)	17 (100.0)	
Duration of NAC administration (days)	42 [42–48]	43 [42–47]	42 [41–43]	0.30
Patients who skipped anticancer drug administration due to AEs	2 (14.3)	2 (14.3)	2 (11.8)	0.97
Patients who required reduction of anticancer drugs due to AEs	3 (21.4)	1 (7.1)	4 (23.5)	0.45
Duration from the completion of NAC to RARC (days)	31.5 [21–41]	36 [24–40]	32 [25–39]	0.88
Best overall response				0.22
Complete response	1 (7.1)	0	3 (17.6)	
Partial response	1 (7.1)	5 (35.7)	6 (35.3)	
Stable disease	11 (78.6)	8 (57.1)	8 (47.1)	
Progressive disease	1 (7.1)	1 (7.1)	0	

Data are presented as n (%) or median [IQR]. AE, adverse event; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; eGFR, estimated glomerular filtration rate; GC, gemcitabine and cisplatin; GCarbo, gemcitabine and carboplatin; IQR, interquartile range; NAC, neoadjuvant chemotherapy; RARC, robot-assisted radical cystectomy; UC, urothelial carcinoma.

Table 2 Surgical outcomes and perioperative complications

Covariates	Standard GC (n=14)	Split-dose GC (n=14)	GCarbo (n=17)	P value
Total operative time (min)	396 [388–415]	423 [366–462]	384 [269–458]	0.29
Operative time for RARC (min)	112 [104–134]	116 [102–142]	108 [100–128]	0.61
Estimated blood loss (mL)	190 [105–340]	180 [100–307]	145 [80–300]	0.76
Blood transfusion	12 (7.1)	2 (14.3)	0	0.28
Intraoperative complication	0	0	1 (5.9)	0.43
Time to liquid (days)	1.0 [1.0–1.0]	1.0 [1.0–1.0]	1.0 [1.0–1.0]	>0.99
Time to diet (days)	3.0 [2.0–3.0]	2.5 [2.0–3.75]	3.0 [2.0–3.0]	0.86
Length of postoperative hospital stay (days)	19 [16–20]	19 [16–21]	19 [15–22]	0.68
Perioperative complications				
Ileus	3 (21.4)	4 (28.6)	2 (11.8)	0.50
Pyelonephritis	3 (21.4)	2 (14.3)	4 (23.5)	0.69
Sepsis	0	0	1 (5.9)	0.43
Pelvic abscess	0	0	0	>0.99
Surgical site infection	0	0	0	>0.99
Lymphorrhea	0	0	0	>0.99
Cardiac disorder	0	0	0	>0.99
Anastomotic leakage	0	0	1 (5.9)	0.43
Anastomotic stricture	0	0	1 (5.9)	0.43

Data are presented as n (%) or median [IQR]. GC, gemcitabine and cisplatin; GCarbo, gemcitabine and carboplatin; IQR, interquartile range; RARC, robot-assisted radical cystectomy.

median time to fluid intake was 1 day (IQR, 1.0–1.0 day), the median time to diet initiation was 3.0 days (IQR, 2.0–3.0 days), and the median length of hospital stay after surgery was 17 days (IQR, 5.0–20.0 days).

Pathological outcomes

Among all the groups, only 1 patient had a positive surgical margin. Pathological CR was achieved in 12 (26.7%) patients and pDS in 19 (42.2 %). There were no significant differences in pCR or pDS according to treatment regimen (*Table 3*).

Oncological outcomes

At the end of the follow-up period, 7 patients (15.6%) died of BCa. Although the median RFS was 49 months [95% confidence interval (CI): 49 to not applicable (NA)] in the standard GC group, this was not observed in the split-dose GC and GCarbo groups. The 1-year RFS was 92.9% (95% CI, 59.158.1–99.0%) in the standard GC group, 82.5% (95% CI, 45.1–95.5%) in the split-GC group, and 49.0% (95% CI, 21.6–71.7%) in the GCarbo group. Although the RFS tended to be shorter in the GCarbo group than that in the other groups, there were no significant differences among the three groups (P=0.052; *Figure 2A*). The median OS was not reached in any of the three groups. The one-year OS rate was 100% (95% CI: NA to NA) in the standard GC group, 80.0% (95% CI: 20.4–96.9%) in the Split-GC group, and 63.5% (95% CI: 33.1–83.0%) in the GCarbo group. The OS also tended to be lower in the GCarbo group than those in the other groups; however, there was no significant difference among the three groups (P=0.13; *Figure 2B*).

Comparison of eGFR before and after NAC

Changes in eGFR are shown in *Table 4*. For each group, the

Table 3 Surgical outcomes and effectiveness of neoadjuvant chemotherapy

Covariates	Standard GC (n=14)	Split-dose GC (n=14)	GCarbo (n=17)	P value
Surgical margin, n (%)				0.43
RM0	14 (100.0)	14 (100.0)	16 (94.1)	
RM1	0	0	1 (5.9)	
pCR, n (%)	4 (28.6)	3 (21.4)	5 (29.4)	0.86
pDS, n (%)	5 (35.7)	6 (42.9)	6 (35.3)	0.81

GC, gemcitabine plus cisplatin; GCarbo, gemcitabine plus carboplatin; RM, surgical resection margin; pCR, pathological complete response; pDS, pathological down-staging.

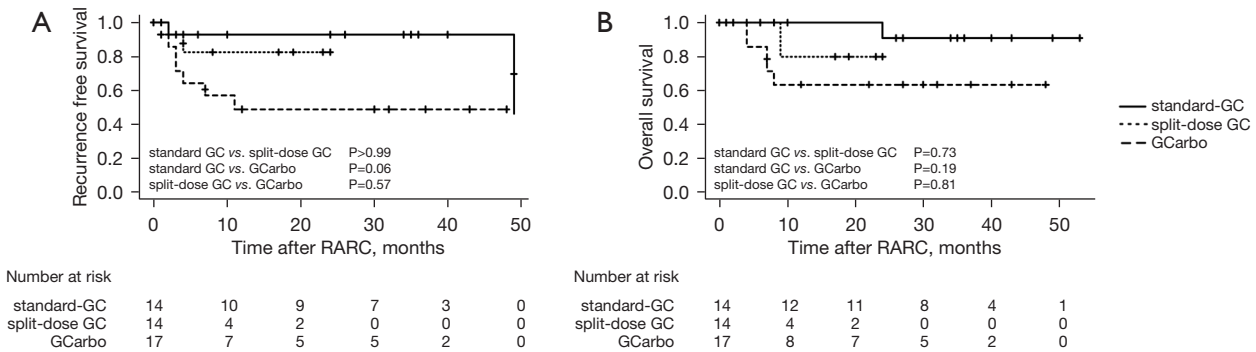

Figure 2 RFS and OS according to chemotherapy regimen. (A) Kaplan-Meier analysis comparing RFS in standard GC, split-dose GC, and GCarbo groups. The 1-year RFS was 92.9% (95% CI, 59.1–99.0%) in the standard GC group, 82.5% (95% CI, 45.1–95.5%) in the split-GC group, and 49.0% (95% CI, 21.6–71.7%) in the GCarbo group. (B) The 1-year OS rate was 100% (95% CI: NA to NA) in the standard GC group, 80.0% (95% CI: 20.4–96.9%) in the Split-GC group, and 63.5% (95% CI: 33.1–83.0%) in the GCarbo group. CI, confidence interval; GC, gemcitabine and cisplatin; GCarbo, gemcitabine and carboplatin; NA, not applicable; OS, overall survival; RFS, recurrence-free survival; RARC, robotic-assisted radical cystectomy.

Table 4 Longitudinal changes in eGFR before and after NAC administration

NAC regimen	eGFR (mL/min/1.73 m^2)				P value
	Before NAC	After NAC	3 months after RARC	6 months after RARC	
Split-dose GC group	65.4 (54.1–71.0)	56.6 (52.7–67.1)	53.3 (47.5–68.2)	50.8 (47.4–66.4)	<0.001
Standard GC group	63.7 (60.0–78.3)	58.0 (49.8–69.4)	52.9 (44.5–63.5)	51.0 (44.1–60.4)	<0.001
GCarbo group	43.4 (36.5–49.9)	43.8 (39.3–51.9)	38.6 (35.4–45.4)	43.6 (38.0–45.9)	0.10

Data are presented as median [IQR]. eGFR, estimated glomerular filtration rate; GC, gemcitabine plus cisplatin; GCarbo, gemcitabine plus carboplatin; IQR, interquartile range; NAC, neoadjuvant chemotherapy; RARC, robot-assisted radical cystectomy.

eGFR was examined before NAC, at the end of NAC, and at 3 and 6 months after RARC. The eGFRs in the standard GC and split-dose GC groups were significantly lower than those before NAC, which continued to decline after surgery (P<0.001). No significant difference in eGFR was observed between the standard GC and split-dose GC groups at any time point with respect to renal function. In the GCarbo group, there were no significant changes in eGFR during the follow-up period.

AEs

The incidence of AEs according to the regimen is shown

Table 5 NAC-related AEs

Adverse event	Standard GC (n=14)	Split-dose GC (n=14)	GCarbo (n=17)	P value
Any grade, n (%)				
Anemia	13 (92.9)	13 (92.9)	16 (94.1)	0.98
Neutropenia	13 (92.9)	13 (92.9)	17 (100.0)	0.53
Thrombocytopenia	14 (100.0)	13 (92.9)	17 (100.0)	0.32
Grade ≥3, n (%)				
Anemia	0	0	3 (17.6)	0.07
Neutropenia	5 (35.7)	6 (42.9)	9 (52.9)	0.92
Thrombocytopenia	6 (42.9)	1 (7.1)	9 (52.9)	0.03

AEs, adverse events; GC, gemcitabine plus cisplatin; GCarbo, gemcitabine plus carboplatin; NAC, neoadjuvant chemotherapy.

in *Table 5*. Although AEs related to hematological toxicity were observed in all the groups, there were no significant differences in their incidence. Thrombocytopenia was significantly lower in the split-GC group than in the other two groups for grade ≥3 AEs.

Discussion

Although RC is the gold standard treatment for MIBC, various combinations of therapies have been attempted, owing to limited improvements in oncologic outcomes with RC alone (2-6). In 2003, Grossman *et al.* (8) conducted an RCT comparing patients with MIBC treated with MVAC as a NAC followed by RC with those treated with RC alone. The median OS was 46 months (95% CI, 25–60) in an RC-alone group and 77 months (95% CI, 55–104) in a NAC group, indicating a trend towards longer OS in patients treated with NAC followed by RC (P=0.006) (8). Furthermore, the proportion of patients who achieved pCR after NAC was 38%, and the 5-year OS was 85%, indicating a good oncological outcome (8). Since the results of this RCT were reported, MVAC therapy has become widely used as an effective treatment for patients with MIBC undergoing RC, in addition to patients with metastatic BCa (7-9,13). However, NAC with MVAC was not performed in all the patients with MIBC because of the high incidence of MVAC-related AEs, particularly hematologic toxicity (31,32). In contrast, an RCT comparing GC and MVAC therapy for locally advanced or metastatic BCa reported comparable OS and incidence of AEs for GC and MVAC therapy (9). Therefore, GC therapy is increasingly performed as NAC, and its outcomes have been validated (10-12,18). In the recently reported GETUG-AFU V05 VESPER trial, dd-MVAC and GC were compared for efficacy as NAC, with patients receiving dd-MVAC having significantly better oncologic outcomes than those receiving GC (13). Although various NAC regimens have been implemented for MIBC, the currently accepted basis for NAC is a cisplatin-based regimen (2,3).

Cisplatin plays an important role in NAC for patients with MIBC; however, good renal function is required for cisplatin administration (2). The National Comprehensive Cancer Network (NCCN) guideline recommends 70 mg/m^2 of cisplatin in a single day in patients with MIBC having normal renal function. For those with impaired renal function, it suggests 35 mg/m^2 of cisplatin in divided doses on days 1 and 8 or days 1 and 2 (2). Several studies have reported the efficacy of split-dose cisplatin regimens. Patients with locally advanced or metastatic urothelial carcinoma (UC) and a creatinine clearance of 35–59 mL/min were treated with gemcitabine 2,500 mg/m^2 and cisplatin 35 mg/m^2 on day 1 and 15 of a 28-day schedule, and their treatment efficacy and AEs were investigated (33). The median age of the enrolled patients was 74 years (range, 51–82 years), the median ECOG-PS score was 1 (range, 0–2), and the median creatinine clearance was 49 mL/min (range, 35–59 mL/min) (33). With a median follow-up of 14.1 months, the median number of cycles of split-GC administration was 3 (range, 1–7) (33). Dose intensity was 85% for gemcitabine and 95% for cisplatin (33). In a study comparing cisplatin 35 mg/m^2 split-dose regimens with the standard dose of 70 mg/m^2 for GC or dd-MVAC chemotherapy, the pCR rate for the split-dose group was 17.5% (95% CI, 7–33%), whereas the pCR rate for the standard regimen group was 32.5% (95% CI, 19–49%) (17). In a multicenter cohort study, patients with MIBC were

administered three to four courses of 35 mg/m^2 of cisplatin in split-dose regimens and a standard dose of 70 mg/m^2 in GC or dd-MVAC regimens, followed by RC, to compare treatment efficacy (17). The pCR rate was 17.5% (95% CI, 7–33%) in the split-dose group and 32.5% (95% CI, 19–49%) in the standard treatment group (17). The proportion of patients with <pT2 was 27.5% (95% CI, 15–44%) in the split-dose group and 45% (95% CI, 29–62%) in the standard treatment group (17). Although patients in the standard treatment group tended to have a better treatment response than those in the split-dose group, there was no statistically significant difference between the two groups (P=0.21 and P=0.21, respectively) (17). Hussain *et al.* (34) investigated patients with MIBC who received fractionated cisplatin-based NAC on days one and eight of a 21-day cycle prior to chemotherapy or RC and those who had an eGFR of ≥40 mL/min. NAC consisted of four cycles of 1,000 mg/m^2 of gemcitabine on days 1, 8, and 21, and 35 mg/m^2 of cisplatin on days 1 and 8 (34). Overall, 13.6% of the patients had early disease progression and did not receive definitive therapy for MIBC. NAC was achieved in 11 (50%) patients with clinical CR after NAC, 9 of whom underwent chemoradiotherapy (34). During a median follow-up of 57 months (range, 4.4–68.5 months) for patients who survived, the three-year survival rate was 37.5% (95% CI, 17–58%), and 5-year survival rate was 31% (95% CI, 15–52%) (34). Although there are few studies on split-dose GC, the pCR and objective response rate (ORR) of patients with MIBC who received split-dose GC were 21.4% and 35.7%, respectively, and the results of this study are comparable to those of previous reports (17,33,34). In our study, the pCR rates of both GC and GCarbo therapy were lower than in the previous report (18). Based on the results of our previous studies (19,20), we performed 2 cycles of NAC followed by RARC. The reason is to reduce the risk of missed surgical opportunities due to possible patient exhaustion from the increased number of NAC cycles and the possibility of PD after the third or fourth cycle. The pCR rate in this study was greater than 20% for any of the NAC regimens. This indicates that several patients were in pCR due to the induction of tumor cell apoptosis, even though the tumor remained on imaging studies. Despite a detailed analysis of the data collected in this study, it was not possible to determine the cause of the higher CR rate in the GCarbo arm.

Currently, Level I evidence comparing cisplatin- and carboplatin-based chemotherapy in patients with BCa is unavailable (19). Oncological outcomes of carboplatin-based regimens in patients with advanced UC are worse than those of cisplatin-based regimens (35,36). Therefore, various guidelines do not recommend NAC with carboplatin in patients with MIBC and impaired renal function (2,3); however, it may be administered as an alternative to cisplatin in daily clinical practice (18,19,21,32,37). In a retrospective cohort study of patients with MIBC who underwent chemoradiation or RC after receiving GC or GCarbo as NAC, the clinical CR and OS according to regimen were compared (18). Carboplatin was administered to patients with an ECOG-PS score of 2, creatinine clearance of <60 mL/min, hydronephrosis, ejection fraction <50%, or those with a single kidney (18). Although the clinical CR rate was 38.7% in the GC group and 36.2% in the GCarbo group, with no significant difference between the two groups (P=0.77), the median OS at a median follow-up of 43 months was significantly longer in the GC group than that in the GCarbo group (41.0 and 26.0 months; P=0.008) (18). However, differences in the NAC regimen were not an independent prognostic factor for OS in a multivariate analysis (18). Murasawa *et al.* (19) conducted a retrospective cohort study of 171 cis-diamminedichloroplatinum (CDDP)-ineligible patients with MIBC who underwent NAC with GCarbo followed by RC and those who underwent RC alone. Five-year OS and RFS rates were 79.5% and 75.5% in the GCarbo group and 53.8% and 55.4% in the RC-alone group, respectively (P<0.001 and P=0.01, respectively) (19). In contrast, a comparison of cisplatin-eligible and-ineligible patients who received GCarbo as NAC at the same time showed that OS was 89.2% and 79.5%, respectively; although there was no significant difference, OS tended to be prolonged in cisplatin-eligible patients (P=0.007) (19). In a multicenter retrospective study on the differential treatment efficacy of cisplatin and carboplatin, the clinical outcomes of patients with MIBC who received at least three courses of cisplatin or carboplatin were compared (38). The pCR rates were 22.1% and 20.7% in the GC and GCarbo groups, respectively, with no significant difference between the two groups (P=0.72) (38). Median OS was 28.6 months (95% CI, 18.1–39.1) in the GC group and 45.1 months (95% CI, 32.7–57.6) in the GCarbo group (P=0.18). Meanwhile, median cancer-specific survival (CSS) was 71.0 months (95% CI, not reached) in the GC group and 28.8 months (95% CI, 9.8–47.8) in the GCarbo group (P=0.02) (38). In the multivariate analysis, the NAC regimen showed no statistically significant difference in OS [hazard ratio (HR), 1.20; 95% CI, 0.85–1.67; P=0.31] and CSS (HR,

1.35; 95% CI, 0.93–1.96; P=0.11) (38). In a randomized trial that directly compared cisplatin and carboplatin in patients with MIBC, ORR was 65.9% in a GC group and 56.4% in a GCarbo group, with median survival of 12.8 and 9.8 months in the GC and GCarbo groups, respectively (36). No statistically significant differences were found between the two groups with respect to ORR and median survival (36). A meta-analysis of randomized trials found that the pooled risk ratio for achieving ORR with cisplatin or carboplatin was 1.34 (P=0.02), while the pooled risk ratio for all-cause mortality at 12 months with cisplatin or carboplatin-based chemotherapy was 0.775 (P=0.12) (39). In this study, there was no significant difference in OS and RFS between gemcitabine-based regimens and GCarbo; however, oncological outcomes tended to be worse in patients with MIBC receiving GCarbo. Therefore, the results of this study suggest that the therapeutic effect of carboplatin-based chemotherapy may be limited with respect to oncological outcomes, which is similar to previous reports (18,19,36-38).

Although the administration of 70 mg/m^2 cisplatin as NAC is recommended in several guidelines (2,3), some patients are required to change the treatment regimen due to AEs, such as renal impairment, during cisplatin-based NAC (17,33,40). The incidence of AEs of any grade in patients receiving NAC was similar in the two groups, and the incidence of nephrotoxicity, defined as an increase in creatinine to 1.5 the baseline at any point during NAC administration (split-dose group, 45%; standard treatment group, 35%) did not differ significantly (P=0.36) (17). Eight percent of the patients discontinued the treatment because of AEs (one grade 3 hepatotoxicity, one grade 3 thrombocytopenia, and one grade 3 anemia), although no ototoxicity or peripheral neuropathy was observed (33). This study examined combination therapy with GC administered at appropriate doses every 2 weeks (33). The dosage schedule of cisplatin used in this study was suggested to be safe and feasible for patients with UC and impaired renal function (33). Although all patients had a creatinine clearance of <60 mL/min, none of the patients' renal function worsened during this treatment (22). A recent study of patients undergoing cisplatin-based NAC found higher pCR rates in those with normal eGFR than those in patients with low eGFR, and there was no difference in GFR change from baseline to post-NAC in the two groups (15). In the area of oropharyngeal cancer, a study on the incidence of renal dysfunction in patients treated with high-dose cisplatin versus split-dose cisplatin found no statistical difference in peak or new baseline creatinine levels between the two groups (40). In both groups, there was no statistically significant association between the dosing schedule and total cumulative dose (40). In this study, both the standard GC and split-dose GC groups showed a decrease in renal function compared to before NAC treatment, whereas the GCarbo group did not show any decrease in renal function. Considering the oncological outcomes in patients with MIBC, cisplatin should be used as an NAC. Further studies are needed to determine the best way to administer cisplatin.

The patients included in the split-dose GC arm of the study exhibited no pathological characteristics, such as the proportion of pure UC. While the pCR rates in this arm tended to be marginally lower than in the other two arms, this disparity did not demonstrate statistical significance. This phenomenon can be attributed to the heterogeneous nature of BCa, which is characterized by variable prognoses and natural histories (41). Although cardiovascular disease (CVD) is a completely different disease, some similarities with cancer have been noted and both may be related (42). A retrospective study of BCa patients treated for bladder cancer at two large centers divided patients into two groups according to whether they had a history of CVD (43). Among the 2,050 patients included in the study, 1,638 (79.9%) were diagnosed with BCa (43). The analysis revealed that age and male patients were identified as independent risk factors for BCa; while smoking cessation and the presence of CVD were found to be protective factors (43). In the present study, no data were collected on underlying diseases or drugs used to treat them, which was deemed an issue for future analysis.

This study has certain limitations. First, this was a retrospective study, not an RCT; thus, a potential bias in treatment selection may exist. Second, the number of patients in each group enrolled in the study was small and the follow-up period was relatively short. Therefore, careful consideration should be given to the interpretation of statistical comparisons of the treatment efficacy and oncological outcomes of the three regimens. Third, two courses of NAC were administered to all the patients, and the optimal number of courses of NAC was not compared in this study. Fourth, the study did not examine patients who required a change in regimen during NAC due to a decline or recovery of renal function; therefore, the effect of changing the NAC regimen on treatment efficacy and oncological outcomes may need to be considered. Fifthly, given that the present study exclusively examined patients

who underwent surgical treatment following NAC, it did not compare non-surgical treatment modalities, including radiation alone, treatment with anticancer drugs alone, or chemoradiotherapy. Finally, NAC was performed in all the patients in this study, and the oncological outcomes were not compared with those of the group treated with RC alone. In particular, the effect of GCarbo on oncological outcomes in patients with impaired renal function remains uncertain.

Conclusions

Standard and split-dose GC revealed statistically equivalent therapeutic efficacies and were comparable in terms of a reduction in renal function. Clinical trials for NAC in combination with immune checkpoint inhibitors in patients with MIBC are currently ongoing. The development of novel regimens that can be administered independently of renal function are potential game-changers for NAC.

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Footnote

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