

Modification of Platinum-based Systemic Chemotherapy for Advanced Urothelial Carcinoma in Patients With Suboptimal Renal Function

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Abstract. *Background/Aim:* Standard chemotherapy for advanced urothelial carcinoma (UC) patients with moderate renal dysfunction has not yet been established. *Patients and Methods:* We retrospectively assessed outcomes of patients with advanced UC who underwent first-line chemotherapy with full-/reduced-dose gemcitabine plus cisplatin (GC-f/GC-r) or full-/reduced-dose gemcitabine plus carboplatin (G-Car-f/G-Car-r) according to renal function. *Results:* Seventy-eight patients were included in this study. The objective response rate was 42%, 30%, 42%, and 27% for the GC-f, GC-r, G-Car-f, and G-Car-r groups, respectively. For the GC-r and G-Car-f groups, the median progression-free survival and the median overall survival was 4.5 vs. 7.0 months ($p=0.07$) and 7.5 months vs. 12.0 months ($p=0.124$), respectively. Grade 3/4 thrombocytopenia occurred more frequently in the GC-r group than the G-Car-f group (80% vs. 38%, $p=0.021$). *Conclusion:* G-Car-f could be more beneficial than GC-r for patients with advanced UC who have moderate renal dysfunction.

Cisplatin-based combination chemotherapy is the standard treatment for patients with unresectable or metastatic urothelial carcinoma (UC) (1, 2). However, the prognosis of

these patients remains poor, with a median overall survival (OS) of 12-15 months (3, 4). In addition, more than 50% of patients with UC are ineligible for optimal doses of cisplatin due to renal dysfunction, poor performance status, advanced age, or comorbidities (5, 6). For cisplatin-unfit patients with UC, several studies have demonstrated the efficacy and safety of alternative regimens, such as carboplatin-based regimens (7, 8), or reduced-dose cisplatin-based regimens (9, 10). However, a consensus for the indication criteria for these regimens based on comparative efficacy and safety data has not yet been reached.

In the present study, we retrospectively analyzed the clinical outcomes of patients who received gemcitabine plus cisplatin (GC) or gemcitabine plus carboplatin (G-Car) as first-line treatment for advanced or metastatic UC patients with moderate renal dysfunction.

Patients and Methods

Study population. This study included patients with advanced or metastatic UC who underwent first-line chemotherapy with GC or G-Car at our institution between August 2002 and August 2018. The data were retrospectively evaluated. Patients who received these chemotherapies in neoadjuvant or adjuvant settings were excluded. All patients provided written informed consent to participate in this study, and the protocol was approved by the Ethics Committee of Kyoto University Hospital (#R1581).

Treatments. Patients were stratified according to Cockcroft–Gault creatinine clearance (CG-CCr) values to receive one of four regimens: full-dose GC (GC-f), reduced-dose GC (GC-r), full-dose G-Car (G-Car-f), or reduced-dose G-Car (G-Car-r). CCr (ml/min) was calculated as: $[140 - \text{age (years)} \times \text{weight (kg)} \times 1 \text{ (male) or } 0.85 \text{ (female)}] / [72 \times \text{serum creatinine (mg/dl)} + 0.2]$ (11, 12). Patients with CCr ≥ 20 -29 ml/min received G-Car-r; those with CCr 30-49 ml/min received GC-r (including GC split, as described below) or G-Car-f, and those with CCr ≥ 50 ml/min received GC-f. Patients with CCr < 20

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ml/min were considered to be unfit for chemotherapy and were not included in the study. Several patients received a reduced or modified dose or regimen due to poor performance status or advanced age.

The GC and G-Car regimens were: GC-f: 4-week cycles of 1,000 mg/m² gemcitabine on days 1, 8, and 15, and 70 mg/m² cisplatin on day 2 (1); GC-r: as for GC-f but the cisplatin dose was reduced to 80%; GC split: 3-week cycles of 1,000 mg/m² gemcitabine on days 1, 8, and 15, and 35 mg/m² cisplatin on either days 2 and 3 or days 2 and 9 (9); G-Car-f: 3-week cycles of 1,000 mg/m² gemcitabine on days 1 and 8, and carboplatin on day 1 at an area under the curve of 4.5 (8, 13); and G-Car-r: as for G-Car-f except for the gemcitabine and carboplatin doses that were reduced to 80%. All chemotherapy regimens continued until disease progression or a severe adverse event (AE) of grade 4 according to the Common Terminology Criteria for Adverse Event (CTCAE) version 4.0. Some patients who experienced moderate AEs (CTCAE grade 3) continued chemotherapy with dose reduction or modification. For statistical evaluation, patients were assigned to the GC-f, GC-r, G-Car-f, or G-Car-r groups according to the dose and regimen of initial chemotherapy.

Assessment of outcomes. Response to treatment was assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (14). The objective response rate (ORR) was defined as the sum of CR and PR rates. Tumor progression was evaluated by computed tomography after every one or two cycles. The grade of hematological and nephrological AEs was evaluated according to CTCAE version 4.0.

Statistical analysis. The primary purpose of the study was to compare efficacy and safety between the GC-r and G-Car-r groups, and the results for patients treated with GC-f and G-Car-r were reviewed for reference. Statistical analyses were performed using JMP® Pro version 15.2 software (SAS Institute, Inc.). Patient characteristics were compared using a Chi-square test and the Mann-Whitney *U*-test. Progression-free survival (PFS) and OS were evaluated using the Kaplan-Meier method with the log-rank test. Changes in blood test results before and after first-line chemotherapy were compared in the GC-r and G-Car-f groups using Wilcoxon's ranked sign test. *p*<0.05 was considered to be statistically significant.

Results

Patient characteristics. Of the 128 patients who underwent chemotherapy for advanced or metastatic UC at our institution, 78 received platinum-based chemotherapy as first-line treatment and were included in this study. Baseline demographic, clinical, and laboratory characteristics are listed in Table I. The number of patients treated with GC-f, GC-r, G-Car-f, and G-Car-r was 33 (42%), 10 (including 2 patients treated with GC split) (13%), 24 (31%), and 11 (14%), respectively.

Thirty-four (43.6%) patients had primary bladder cancer, of whom 20 (59%) received GC-f. The remaining 44 (56.4%) patients had primary urinary upper tract cancer (UTUC), of whom 13 (30%) received GC-f. The lower

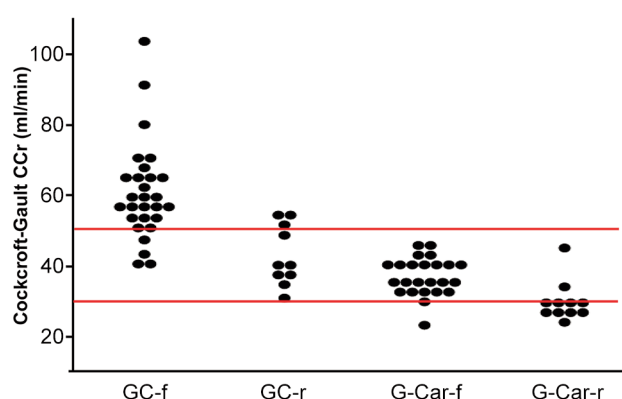


Figure 1. Cockcroft-Gault creatinine clearance (CG-CCr) for patients in the four treatment groups. GC-f: Full-dose gemcitabine plus cisplatin (*n*=33); GC-r: reduced-dose gemcitabine plus cisplatin (*n*=10); G-Car-f: full-dose gemcitabine plus carboplatin (*n*=24); G-Car-r: reduced-dose gemcitabine plus carboplatin (*n*=11). Red lines indicate CG-CCr values of 30 and 50 ml/min.

frequency of GC-f-fit patients for the primary UTUC group compared with the primary bladder cancer group was significant (*p*=0.009). Comparing the GC-r and G-Car-f groups, there were no differences in gender, age, body mass index, primary tumor site, treatment with radical surgery, Eastern Cooperative Oncology Group Performance Status, or number of metastasis sites. CG-CCr was also not significantly different between the GC-r and the G-Car-f group (Figure 1, Table I). However, the neutrophil to lymphocyte ratio (NLR; *p*=0.02), white blood cell (WBC) count (*p*=0.009), and C-reactive protein (CRP) concentration (*p*=0.008) were significantly higher in the GC-r group than the G-Car-f group (Table I).

Efficacy. The median PFS for the GC-f, GC-r, G-Car-f, and G-Car-r groups was 6.0, 4.5, 7.0, and 4.0 months, respectively (Figure 2, left), and the median OS was 14.0, 7.5, 12.0, and 7.0 months, respectively (Figure 2, right). There was no significant difference between the GC-r and G-Car-f groups in either PFS (*p*=0.07) or OS (*p*=0.124).

The best objective response to first-line chemotherapy for each treatment group is shown in Figure 3. The ORR for GC-f, GC-r, G-Car-f, and G-Car-r groups was 42%, 30%, 42%, and 27% respectively. The PD rate was 50% for the GC-r group and 25% for the G-Car-f group (*p*=0.232, Fisher's exact test).

Dose administration. First-line chemotherapy was discontinued within 1-3 cycles in 42%, 60%, 42%, and 55% of patients in the GC-f, GC-r, G-Car-f, and G-Car-r groups, respectively (*p*=0.457 for GC-r vs. G-Car-f, Fisher's exact test, Figure 4). Notably, 50% (*n*=5) of patients in the GC-r group discontinued chemotherapy after the first course due to PD (*n*=3), nephrotoxicity (*n*=1), or hepatotoxicity (*n*=1).

Table I. Clinical and demographic characteristics of the 78 study patients.

Characteristics	GC-f, n (%) (n=33)	GC-r, n (%) (n=10)	G-Car-f, n (%) (n=24)	G-Car-r, n (%) (n=11)	<i>p</i> -Value (GC-r vs. G-Car-f)
Gender					0.23
Male	30 (91)	9 (90)	17 (71)	5 (45)	
Female	3 (9)	1 (10)	7 (29)	6 (55)	
Age, years, median (range)	65 (45-80)	71.5 (56-80)	73 (60-82)	79 (65-85)	0.609
BMI, kg/m ² , median (range)	22.9 (17.6-32.3)	21.5 (17.1-27.3)	22 (17-27.7)	20.6 (16-27)	1.000
Primary tumor site					0.711
Bladder	20 (61)	4 (40)	8 (33)	2 (18)	
Urinary upper tract	13 (39)	6 (60)	16 (67)	9 (82)	
Radical surgery	11 (33)	5 (50)	12 (50)	5 (45)	1.000
ECOG PS					0.128
0	14 (42)	1 (10)	3 (13)	1 (9)	
1	12 (36)	6 (60)	20 (83)	7 (64)	
≥2	7 (21)	3 (30)	1 (4)	4 (36)	
Site of metastasis, n					
Lung	10 (30)	5 (50)	7 (29)	6 (55)	0.247
Liver	3 (9)	1 (10)	4 (17)	2 (18)	0.606
Bone	6 (18)	4 (40)	5 (21)	1 (9)	0.248
Lymph node	21 (64)	5 (50)	18 (75)	8 (73)	0.156
Others	2 (6)	1 (10)	1 (4)	1 (9)	0.51
No. of metastatic sites, n					
≤1	21 (64)	4 (40)	13 (54)	6 (55)	6 (55)
≤2	12 (36)	6 (60)	11 (46)	5 (45)	5 (45)
Blood test data, median					
NLR	3.1	8.4	3.1	4.5	0.01
Hb, g/dl	12.5	11.1	12.1	10.4	0.249
WBC, ×10 ³ /μl	7.2	10.1	6.5	6.3	0.007
Plt, ×10 ⁴ /μl	24.8	27.9	25.8	23.3	0.484
Cre, mg/dl	0.9	1.3	1.2	1.1	0.746
CG-CCr, ml/min	58.1	39	35	27.7	0.108
CRP, mg/dl	0.7	3.3	0.4	0.8	0.008

GC-f: Full-dose gemcitabine plus cisplatin; GC-r: reduced-dose gemcitabine plus cisplatin; G-Car-f: full-dose gemcitabine plus carboplatin; G-Car-r: reduced-dose gemcitabine plus carboplatin; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; NLR: neutrophil to lymphocyte ratio; Hb: hemoglobin; WBC: white blood cell; Plt: platelet; Cre: creatinine; CG-CCr: Cockcroft–Gault creatinine clearance; CRP: C-reactive protein. *p*-Values were determined by the Chi-square test and Mann-Whitney *U*-test.

In total, first-line chemotherapy was discontinued due to AEs in 18%, 30%, 17%, and 18% of patients in the GC-f, GC-r, G-Car-f, and G-Car-r groups, respectively ($p=0.394$ for GC-r vs. G-Car-f, Fisher's exact test, Figure 4).

Toxicity. The number of patients who experienced CTCAE grade 3-4 hematologic AEs is shown in Table II. Grade 3-4 thrombocytopenia was significantly more frequent in the GC-r group than the G-Car-f group (80% vs. 38%, $p=0.021$), but no other significant differences in hematologic AEs were detected. Regarding nephrotoxicity, serum creatinine concentrations did not differ before and after first-line chemotherapy for either the GC-r group or G-Car-f group (Figure 5), although one patient developed acute kidney injury after the first course of GC-r, leading to discontinuation

of the chemotherapy. All five patients in the GC-r group who discontinued chemotherapy after the first cycle had relatively high pretreatment serum creatinine concentrations (Figure 5).

Other measures. Because we previously reported that NLR is a prognostic factor for subsequent pembrolizumab treatment after first-line chemotherapy in UC patients (15), we also evaluated NLR in the present study. As shown in Figure 6, we detected no significant changes in NLR in the GC-r group ($p=0.695$) or G-Car-f group ($p=1.000$).

Discussion

Cisplatin-based chemotherapy is the gold standard in the first-line treatment of patients with advanced or metastatic

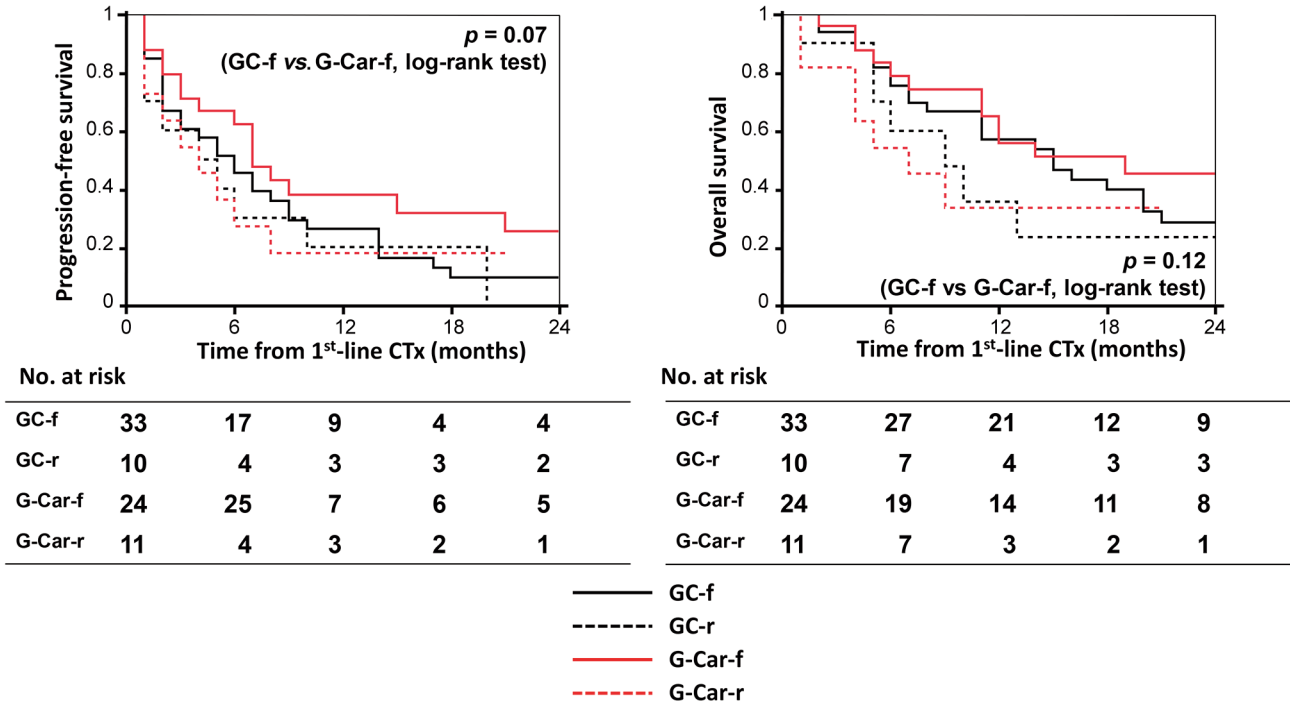


Figure 2. Kaplan-Meier curves for progression-free survival (PFS, left) and overall survival (OS, right) of patients in the four treatment groups. GC-f: Full-dose gemcitabine plus cisplatin; GC-r: reduced-dose gemcitabine plus cisplatin; G-Car-f: full-dose gemcitabine plus carboplatin; G-Car-r: reduced-dose gemcitabine plus carboplatin; Ctx: chemotherapy.

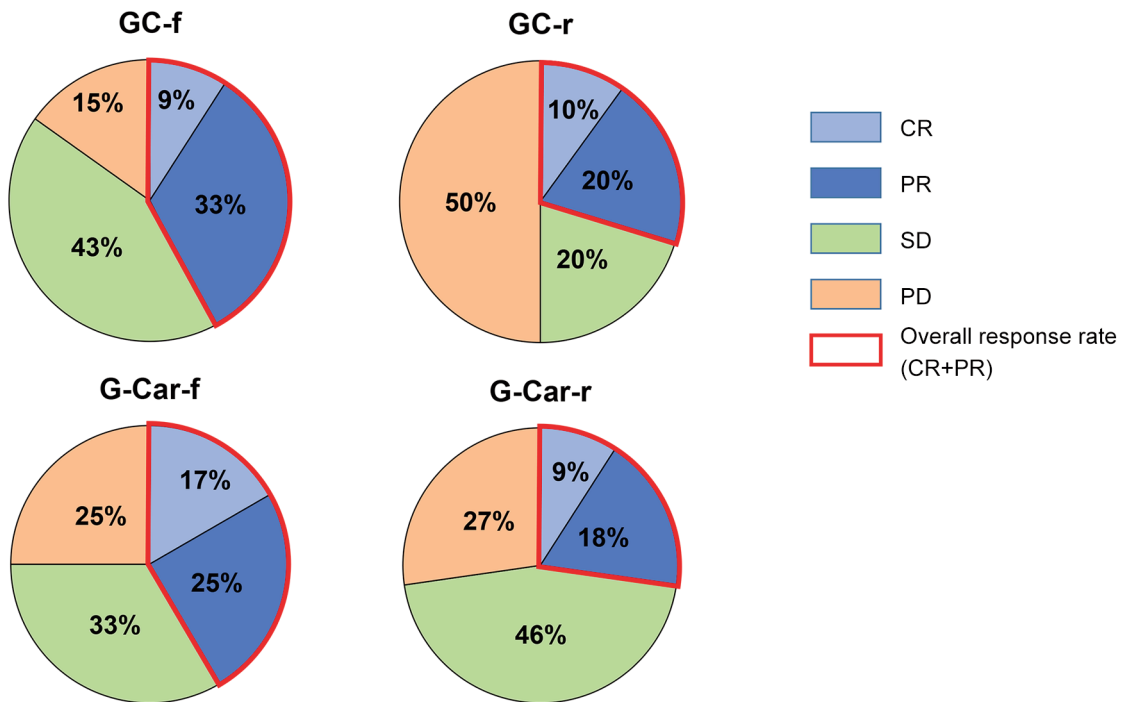


Figure 3. Best objective responses in tumor size for patients in the four treatment groups. GC-f: Full-dose gemcitabine plus cisplatin (n=33); GC-r: reduced-dose gemcitabine plus cisplatin (n=10); G-Car-f: full-dose gemcitabine plus carboplatin (n=24); G-Car-r: reduced-dose gemcitabine plus carboplatin (n=11); CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

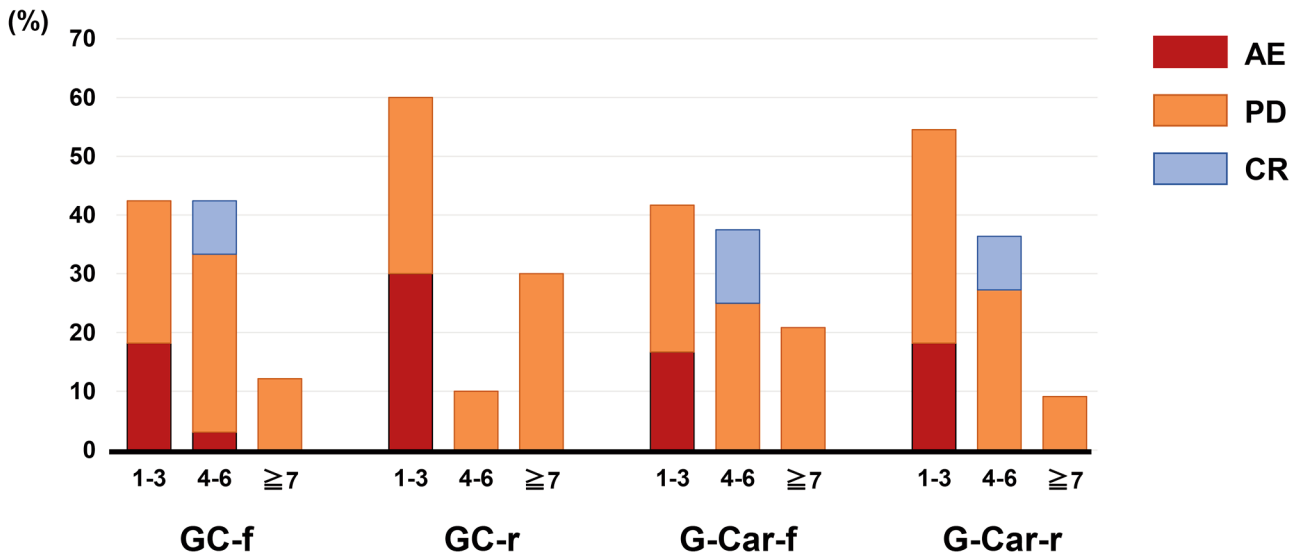


Figure 4. Cycles of treatment completed before discontinuation for the four treatment groups. GC-f: Full-dose gemcitabine plus cisplatin (n=33); GC-r: reduced-dose gemcitabine plus cisplatin (n=10); G-Car-f: full-dose gemcitabine plus carboplatin (n=24); G-Car-r: reduced-dose gemcitabine plus carboplatin (n=11); AE: adverse event; CR: complete response; PD: progressive disease.

Table II. Grade 3-4 hematologic adverse events.

Characteristics	GC-f, n (%) (n=33)	GC-r, n (%) (n=10)	G-Car-f, n (%) (n=24)	G-Car-r, n (%) (n=11)	p-Value (GC-r vs. G-Car-f)
Leukopenia	3 (9)	4 (40)	8 (33)	2 (18)	0.712
Neutropenia	13 (39)	5 (50)	9 (38)	3 (27)	0.502
Thrombocytopenia	10 (30)	8 (80)	9 (38)	4 (36)	0.021
Anemia	5 (15)	3 (30)	7 (29)	5 (45)	0.961

GC-f: Full-dose gemcitabine plus cisplatin; GC-r: reduced-dose gemcitabine plus cisplatin; G-Car-f: full-dose gemcitabine plus carboplatin; G-Car-r: reduced-dose gemcitabine plus carboplatin. p-Values were determined by the Chi-square test.

UC. However, a large proportion of patients are ineligible for cisplatin therapy due to renal dysfunction, age, poor performance status, or comorbidities affecting other organs (16). In the present study, 58% of the 78 patients were ineligible for full-dose cisplatin according to our indication criteria. The proportion of cisplatin-unfit patients was larger for patients with primary UTUC than for patients with primary bladder cancer, probably due to greater renal impairment.

The proportion of patients ineligible for full-dose cisplatin in the present study is higher than the corresponding rate of 28% observed in a previous study of UC patients (17). This difference is likely to be due, at least in part, to the older age of our patients; indeed, this would be consistent with the finding by Dash *et al.* (17) that more than 40% of their elderly patients (aged >70 years) were ineligible for full-dose cisplatin treatment.

Our strategy of allocating chemotherapy regimens according to CG-CCr was partially based on the Galsky criteria for selecting patients eligible for cisplatin-based chemotherapy (5). Although the Galsky criteria defines patients with CG-CCr <60 ml/min as unfit for cisplatin therapy, we administered full-dose GC to patients with CG-CCr 50-60 ml/min and found that it was efficacious and safe. Patients with CG-CCr <50 ml/min who were treated with G-Car-f showed better ORR, PFS, and OS than those treated with GC-r. Our results are consistent with the results of previous studies reporting an ORR of 36.0-60.8% and median OS of 7.2-15.4 months for UC patients treated with G-Car (7, 8, 13, 18-20).

We found that treatment discontinuation within 3 cycles and grade 3/4 hematological toxicity were most common among patients in the GC-r group. In particular, 50% (n=5) of the patients in the GC-r group discontinued treatment after

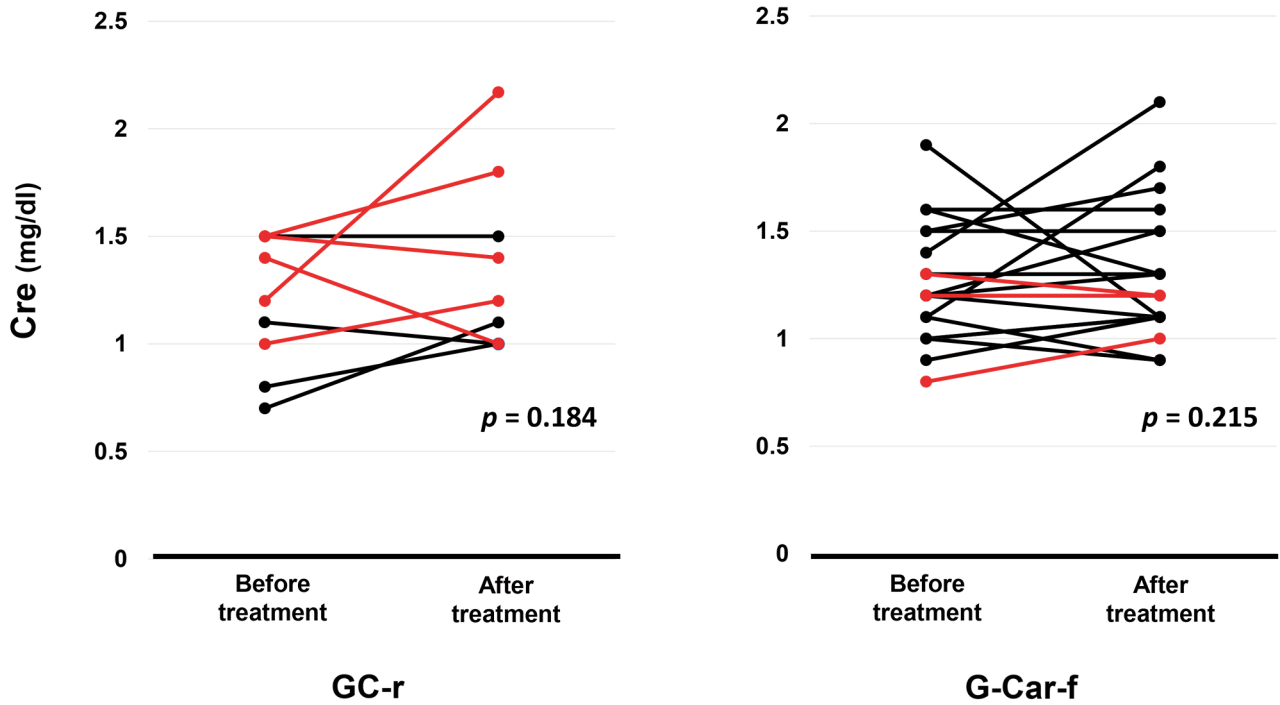


Figure 5. Serum creatinine (Cre) concentrations before and after first-line chemotherapy for patients treated with reduced-dose gemcitabine plus cisplatin (GC-r, n=10) or full-dose gemcitabine plus carboplatin (G-Car-f, n=24). Patients who discontinued the regimen after the first cycle are shown in red. p-Values were determined by the Wilcoxon ranked sign test.

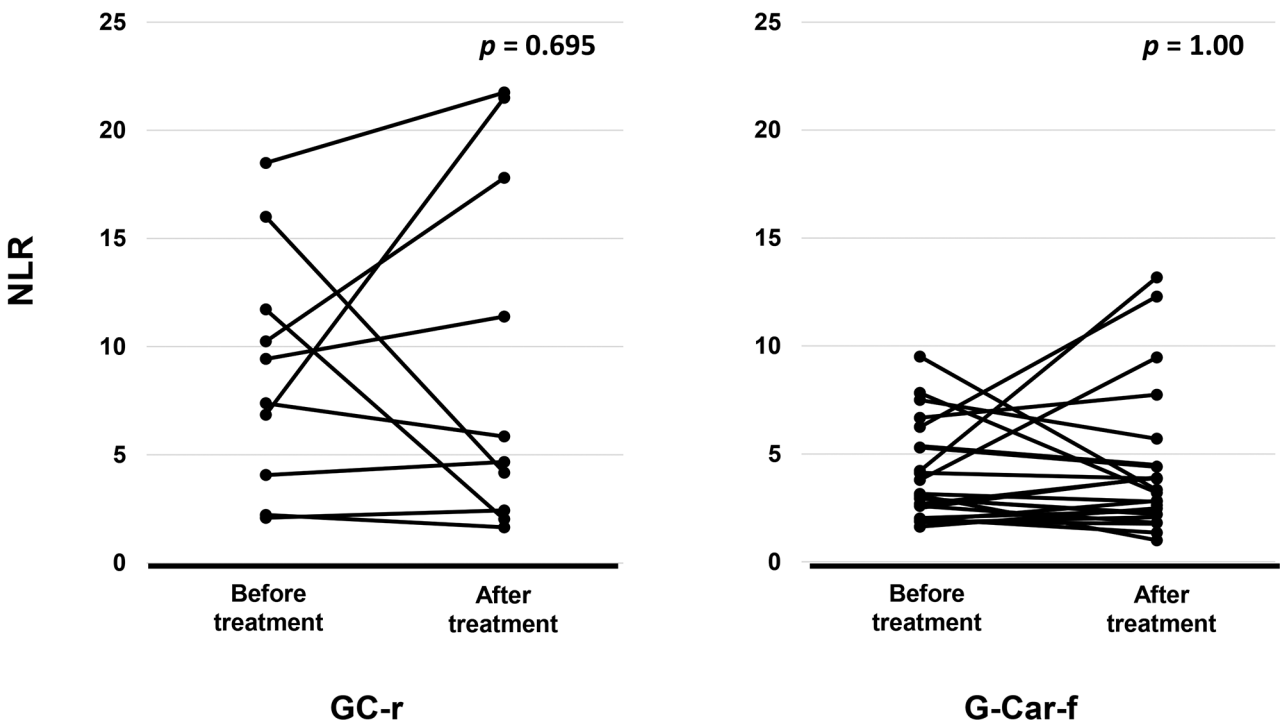


Figure 6. Neutrophil to lymphocyte ratio (NLR) before and after first-line chemotherapy for patients treated with reduced-dose gemcitabine plus cisplatin (GC-r, n=10) or full-dose gemcitabine plus carboplatin (G-Car-f, n=24). p-Values were determined by the Wilcoxon ranked sign test.

the first cycle. These findings suggest that the dose intensity of G-Car-f, which was based on CG-CCr according to the Calvert formula, was associated with a more favorable safety profile compared with the fixed dose based on body surface area in GC-r.

Two earlier studies compared G-Car with GC split for UC patients with marginally impaired renal function, and reported more favorable response and tolerability of GC split compared with G-Car (21, 22). However, these studies were inconclusive due to the small sample sizes. In the present study, G-Car-f gave results comparable to GC-f, but G-Car-f may be more beneficial than GC-r to patients with CCr <50 ml/min in terms of both efficacy and safety. This discrepancy between the previous studies and ours may be attributed to differences in patient clinicopathological characteristics, including renal function and treatment indication. Further data must be obtained before a final consensus can be reached on the optimal treatment regimen for UC patients with marginal renal dysfunction.

Immune checkpoint inhibitors have improved the survival of patients with advanced UC (23, 24). Although cisplatin-based chemotherapy is still recommended for cisplatin-eligible patients, atezolizumab and pembrolizumab, which target the PD-L1–PD-1 checkpoint, are recommended as first-line therapy options for patients with locally advanced or metastatic disease who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression (25). However, only 20-30% of patients with advanced UC exhibit PD-L1 overexpression (26, 27) and the use of immune checkpoint inhibitors as first-line treatment has not yet been approved in Japan. Therefore, platinum-based chemotherapy still represents the backbone of first-line treatment for a majority of patients, and there remains a strong need to determine the optimal regimen or dose control for cisplatin-ineligible patients with renal dysfunction.

NLR and hemoglobin (Hb) concentrations have been reported to be associated with oncological outcomes of UC patients receiving second-line pembrolizumab (15). In the present study, however, we detected no significant changes in NLR or Hb (data not shown) before and after first-line chemotherapy for patients treated with GC-r or G-Car-f.

There are several limitations to this study. The patient number was small and they were selected from a single institution. Although we excluded patients who received chemotherapies in neoadjuvant or adjuvant settings, perioperative chemotherapy may have influenced the AE findings to some extent. In addition, the baseline characteristics of patients in the four groups were not distributed evenly because of the retrospective nature of the study. In particular, NLR, WBC, and CRP were significantly higher in the GC-r group than the G-Car-f group, suggesting

that patients in the GC-r group may have had a more aggressive advanced UC. Randomized studies with larger populations may be required to confirm our observations. It is unclear whether our results can be applicable to UC patients receiving other chemotherapeutic regimens (28, 29).

In conclusion, our data suggest that G-Car-f may be more beneficial than GC-r for patients with advanced or metastatic UC who have moderate renal dysfunction. Additional data will be needed to confirm the optimal indication criteria for cisplatin-ineligible patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Author's Contributions

All Authors of this research paper have directly participated in the planning, execution, or analysis of the study. All Authors of this paper have read and approved the final version submitted.

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