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Impact of renal function of patients with advanced urothelial cancer on eligibility for first-line chemotherapy and treatment outcomes

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Abstract

Objective: The aim of the study is to clarify the clinical effects of first-line chemotherapy regimens for advanced urothelial cancer on clinical responses and survival of patients grouped by renal function.

Methods: In this multicenter retrospective cohort study, 345 urothelial cancer patients received systemic chemotherapy for metastatic or unresectable disease in 17 centers (2004–10).

Results: Two hundred and forty-one patients were treated with methotrexate, vinblastine, doxorubicin and cisplatin/methotrexate, epirubicin and cisplatin ($n = 136$) or gemcitabine and cisplatin ($n = 105$) followed by carboplatin-based treatments, non-platinum treatments or other regimens. After 2008, gemcitabine and cisplatin was the most frequently used regimen in patients with an estimated glomerular filtration rate <60 ml/min/1.73 m^2 and in those with estimated glomerular filtration rate ≥60 ml/min/1.73 m^2. The gemcitabine and cisplatin patients' complete response rate was 10.5% and their response rate was 52.4%, which was highest among all regimens. Gemcitabine and cisplatin demonstrated a better 3-year overall survival when the estimated glomerular filtration rate was ≥60 ml/min/1.73 m^2 (31.4%), but it tended to be worse when the estimated glomerular filtration rate was <60 ml/min/1.73 m^2 (14.1%). In the latter cases, the dose reduction rate of gemcitabine and cisplatin was high (43.9%). Among the patients with estimated glomerular filtration rate <60 ml/min/1.73 m^2, the 1-year overall survival of the patients treated with a reduced dose of gemcitabine and cisplatin was significantly lower than that of those treated with standard-dose gemcitabine and cisplatin (26.2 vs. 60.3%, respectively, $P = 0.0108$).

Conclusions: Gemcitabine and cisplatin provided favorable responses and survival in patients with estimated glomerular filtration rate ≥60 ml/min/1.73 m^2 but unsatisfactory oncological outcomes in patients with estimated glomerular filtration rate <60 ml/min/1.73 m^2, especially when treated with a reduced dose. Alternative regimens might be optimal rather than reduced-dose gemcitabine and cisplatin in patients with estimated glomerular filtration rate <60 ml/min/1.73 m^2.

Key words: urothelial cancer, gemcitabine, cisplatin, renal function, chemotherapy, eGFR

Introduction

Urothelial cancer (UC) is derived from the epithelium of the bladder and the upper urinary tract, including the renal pelvis and the ureter. When UC cases are localized disease, surgical treatments including endoscopic surgery, radical cystectomy and nephroureterectomy are the gold standard. When UC patients develop metastases, their prognoses remain unsatisfactory even if they are treated with systemic chemotherapy. The MVAC regimen (methotrexate, vinblastine, doxorubicin and cisplatin) was used initially as the first-line chemotherapy for metastatic UC (1). Gemcitabine and cisplatin (GC) have become a standard chemotherapy, after a large and multinational randomized clinical trial (RCT) comparing MVAC and GC indicated in 2000 that GC had similar oncological efficacy and a lower toxicity profile for advanced UC (2). In Japan as well, GC has been widely used as the first-line chemotherapy for UC since the use of gemcitabine for UC began being reimbursed by the government in 2008.

One of the issues regarding systemic chemotherapy for advanced UC is how to treat UC patients with renal impairment, because cisplatin, a key drug in both regimens, is nephrotoxic. A higher prevalence of chronic kidney disease (CKD) among genitourinary cancer patients was demonstrated, with the introduction of the concept of CKD defined by the estimated glomerular filtration rate (eGFR) equations (3,4). Vaughn (5) reported that ~40% of bladder cancer patients were judged to be cisplatin-ineligible due to renal impairment. Due to this high prevalence of renal impairment, a number of clinical studies (6–13) have been conducted in attempts to evaluate the feasibility and efficacy of an alternative chemotherapy regimen to standard regimens such as GC and MVAC. Two major approaches are employed: one is to use a reduced dose or split doses of cisplatin (6,7), and the other is the substitution of carboplatin for cisplatin (8–13). Although some promising results were reported, sufficient evidence of the outcomes of these alternative regimens compared with the original cisplatin-based regimen has not yet been published, to our knowledge.

We conducted the present multicenter retrospective cohort study of 345 Japanese UC patients who received systemic chemotherapy for metastatic or unresectable disease, to clarify how to select the first-line chemotherapy regimen according to renal function and to determine the impact of regimens on clinical responses and survival.

Patients and methods

Patients

Three hundred and forty-five patients with advanced or unresectable UC who received systemic chemotherapy were treated at 17 hospitals in Japan between January 2004 and December 2010. Patients who received perisurgical chemotherapy (neoadjuvant or adjuvant chemotherapy) and those who received chemoradiation for bladder preservation were excluded. All of the cases required the pathological confirmation of UC except for the patients with upper urinary tract cancer, who were diagnosed based on the results of positive urinary cytology and radiological examinations. All data were collected from medical records in each institution and registered by a secretariat server over the Internet.

The data at the start of chemotherapy included the patient's age, height and weight, gender, performance status (PS), comorbidity, TNM stage, site of metastases, the status of the kidneys and serum creatinine levels. In addition, the regimen of each patient's first-line chemotherapy, the planned dose of each drug and the presence or absence of dose reduction at the start of chemotherapy were recorded and analyzed. The definition of dose reduction depended on the physician who treats each patient. The follow-up status data were collected in December 2013. The median follow-up duration was 10.4 months (range 1–97 months). The observed toxicities during the induction chemotherapy were graded according to CTCAE v4.0. This retrospective study was approved by the internal ethical committees at all 17 institutions.

The backgrounds of the 345 patients are presented in Table 1. The median age was 70 years (range 35–85 years), and 27.8% of the patients were ≥75 years. The primary sites were the bladder in 162 patients (47.0%), the upper urinary tract in 161 patients (46.7%) and both in 22 patients (6.3%). Approximately 94% of the patients had metastatic disease at the start of chemotherapy. Of them, 111 (32.2%) patients had lymph node metastasis only and 213 (61.7%) patients had metastases other than lymph node metastasis. One

Table 1. Characteristics of the 345 urothelial cancer patients

Parameter	No.	%
All patients	345	
Age		
Median (range), years	70 (35–85)	
≥75 years	96	27.8
<75 years	249	72.2
Male	245	71.0
Performance status (PS)		
0–1	323	93.6
≥2	22	6.4
Tumor location		
Bladder	162	47.0
Upper urinary tract	161	46.7
Both	22	6.3
Metastatic sites		
None	21	6.1
Lymph node	111	32.2
Other than lymph node	213	61.7
eGFR		
Median (range), ml/min/1.73 m^2	55.16 (3.58–133.69)	
≥60 ml/min/1.73 m^2	145	42.0
<60 ml/min/1.73 m^2	200	58.0

eGFR, estimated glomerular filtration rate.

hundred and fifty-seven patients had normal kidneys. The other 188 patients (54.5%) had a kidney abnormality including unilateral hydronephrosis (94 patients), bilateral hydronephrosis (22 patients) and solitary kidney (72 patients).

Since this was a retrospective study, the chemotherapy regimens were selected in a general practice manner depending on each institution or each physician. The most frequently selected first-line regimen was GC (105 patients), followed by MVAC ($n = 100$), methotrexate, epirubicin and cisplatin (MEC) ($n = 36$), gemcitabine and carboplatin (GCarbo; $n = 25$), gemcitabine and paclitaxel (GP; $n = 28$), gemcitabine, docetaxel and carboplatin (GDCarbo; $n = 22$) and other treatments in 29 patients. Other miscellaneous treatments included gemcitabine, docetaxel and cisplatin; gemcitabine and nedaplatin; gemcitabine monotherapy and others.

We divided the 345 patients into five groups according to the first-line chemotherapy they received, as follows: (i) the GC group and (ii) the MVAC/MEC group as cisplatin-based treatments, (iii) the GCarbo/GDCarbo group as carboplatin-based treatments, (iv) the GP group as a non-platinum treatment and (v) the other/miscellaneous treatment group.

The patients' clinical responses after the first-line chemotherapy were evaluated as follows. Investigators were asked to report the observed best response during or after the first-line chemotherapy. However, the method of radiological examination and the timing of the response evaluation depended on each institution or each physician. Complete response (CR) was defined as the complete disappearance of all clinical and radiographic findings of UC. Partial response (PR) was defined as a ≥50% reduction in the sum of the products of the greatest perpendicular dimensions of all measurable lesions. Progressive disease (PD) was defined as an increase of ≥25% in the sum of the products of the greatest perpendicular dimensions of all lesions, or the appearance of any new lesion. No change (NC) was defined as disease that did not meet any of the above criteria. Survival was measured from the first day of the patient's chemotherapy.

Evaluation of renal function and statistical analysis

The eGFR was calculated using the formula reported by Matsuo et al. (14). This equation was originated from the Modification of Diet in Renal Disease (MDRD) study group (15), and was adjusted for Japanese

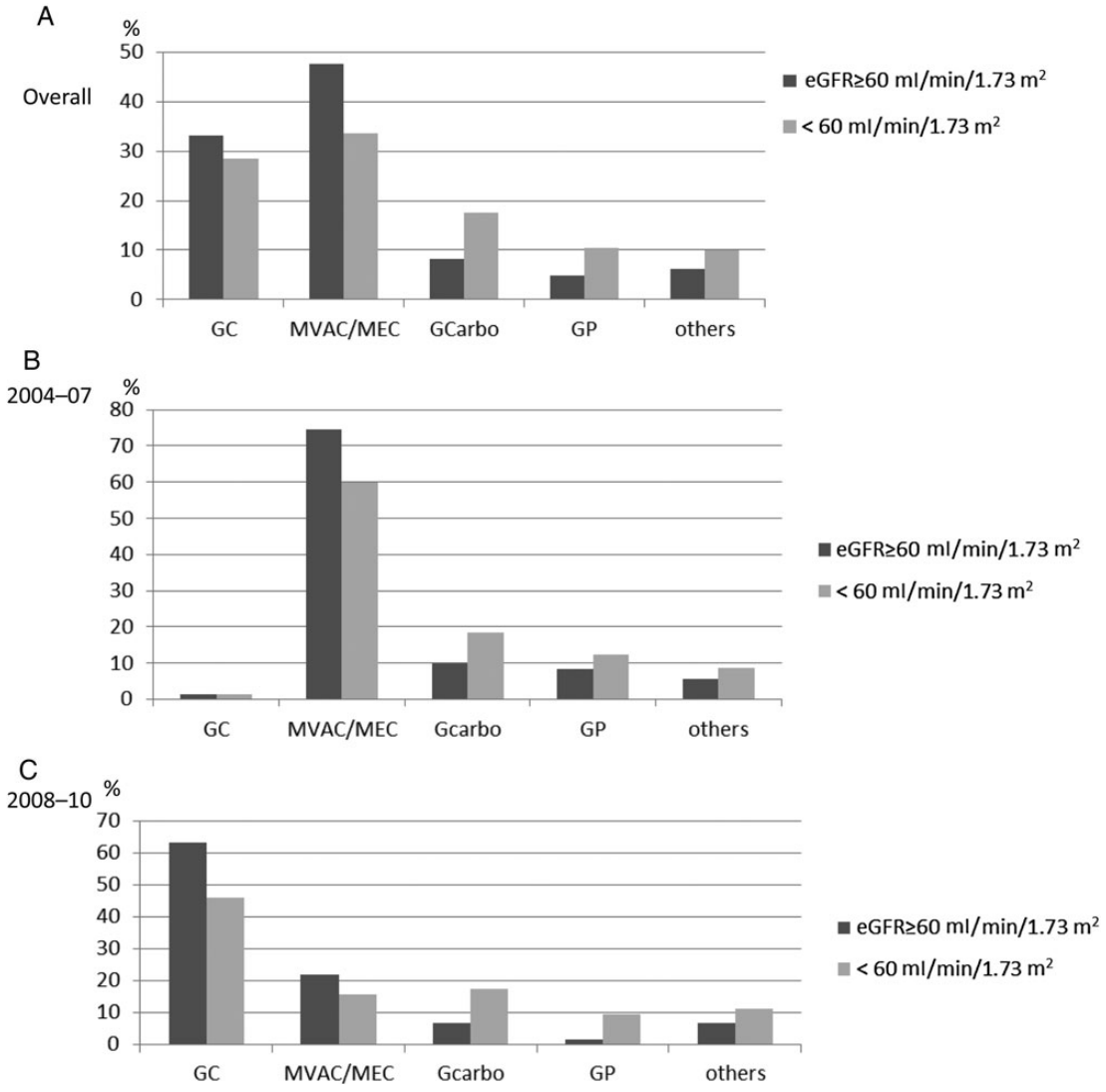

Figure 1. First-line chemotherapy according to renal function.

individuals as recommended by the Japanese Society of Nephrology: eGFR (ml/min/1.73 m^2) = 194 × SerumCr − 1.094 × age (years) − 0.287. The median eGFR of our patients at the start of chemotherapy was 55.2 ml/min/1.73 m^2 (range, 3.6–133.7 ml/min/1.73 m^2). Among the 345 patients, 145 (42%) had an eGFR ≥60 ml/min/1.73 m^2, and the other 200 patients (58%) had an eGFR <60 ml/min/1.73 m^2.

We constructed survival curves by the Kaplan–Meier method and compared them using the generalized Wilcoxon test. The level of significance was set at $P < 0.05$. Statistical analyses were performed using JMP®9 software (SAS Institute, Cary, NC, USA).

Results

Selection of first-line chemotherapy regimen stratified by renal function

Among the 345 patients enrolled, 241 were treated with MVAC/MAC ($n = 136$) or GC ($n = 105$). The other 104 patients were treated with GCarbo/GDCarbo ($n = 47$), GP ($n = 28$) or other miscellaneous regimens ($n = 29$).

When the patients were stratified by eGFR, as shown in Figure 1A, 117 (80.7%) of the 145 patients with eGFR ≥60 ml/min/1.73 m^2 were treated with MVAC/MEC (47.6%) or GC (33.1%) during the overall study period. In contrast, 124 (62.0%) of the 200 patients with eGFR<60 ml/min/1.73 m^2 were treated with MVAC/MEC (33.5%) or GC (28.5%).The proportion of patients with eGFR values <60 ml/min/1.73 m^2 tended to be higher in the years 2008–10 compared with the years 2004–07 (61.2 and 53.6%, respectively), although the difference was not significant.

We compared the selection pattern of first-line chemotherapy between before and after 2008, when the use of gemcitabine for UC began to be reimbursed by public insurance in Japan. As shown in

Table 2. Response and survival according to regimens

Regimen	*n*	Responses		3-year OS (%)
		CR (%)	CR + PR (%)	
GC	105	10.5	52.4[a]	22.0
MVAC/MEC	136	8.1	35.3[a,b]	16.0
GCarbo/GDCarbo	47	4.3	51.1[b]	14.0
GP	28	0	39.3	5.2
Others	29	6.9	27.6	7.2

CR, complete response; PR, partial response; OS, overall survival, GC, gemcitabine and cisplatin; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; MEC, methotrexate, epirubicin and cisplatin; GCarbo, gemcitabine and carboplatin; GDCarbo, gemcitabine, docetaxel and carboplatin.

[a]$P = 0.008$, GC vs. MVAC/MEC.

[b]$P = 0.058$, GCarbo/GDCarbo vs. MVAC/MEC.

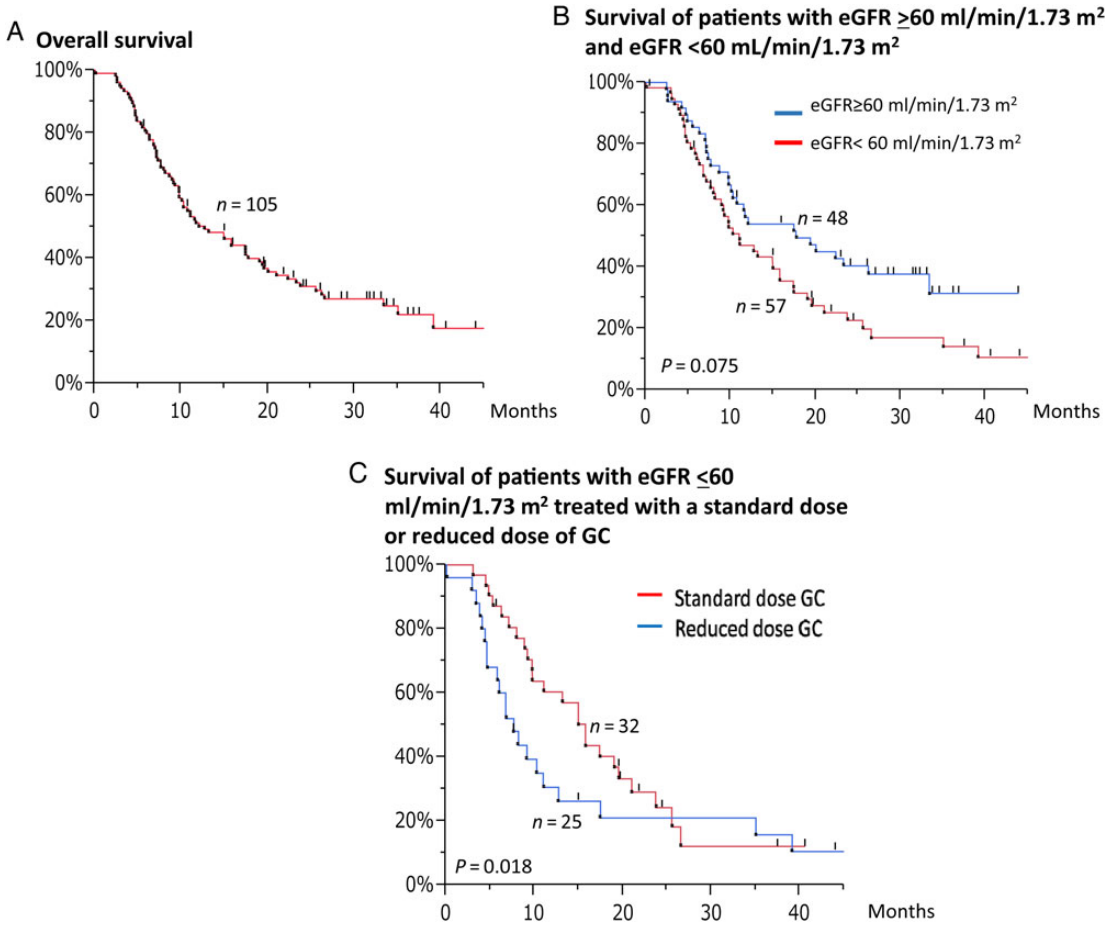

Figure 2. Survival of patients treated with gemcitabine and cisplatin (GC). (A) Overall survival. (B) Survival of patients with estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2 and eGFR <60 ml/min/1.73 m^2. (C) Survival of patients with eGFR <60 ml/min/1.73 m^2 treated with a standard dose or reduced dose of GC.

Figure 1B and C, MVAC/MEC was the most frequently selected regimen irrespective of renal function between 2004 and 2007, whereas the most frequently selected regimen between 2008 and 2010 was GC.

The rates of dose reduction were 25.7% in the GC-treated patients and 21.3% in those treated with MVAC/MEC as the first course of chemotherapy. The dose reduction rate was significantly higher in the patients with eGFR <60 ml/min/1.73 m^2 compared with the patients with eGFR ≥60 ml/min/1.73 m^2 (39.0 and 9.7%, respectively, $P < 0.001$).

Among the patients with eGFR <60 ml/min/1.73 m^2, 25 of 57 (43.9%) and 23 of 67 (34.3%) patients needed a dose reduction at the first course of GC and MVAC/MEC, respectively. The most-often reduced drugs were cisplatin in 30 cases, followed by methotrexate in 10 cases and gemcitabine in four cases and doxorubicin in four cases each ($n = 48$). In 43 (90.0%) of these 48 cases, the reason for dose reduction was renal impairment.

Oncological outcomes of first-line chemotherapy stratified by renal function

As shown in Table 2, the CR rate in the GC group was 10.5%, which was highest among all regimens, followed by MVAC/MEC (8.1%) and GCarbo/GDCarbo (4.3%). No CR was observed among the patients treated with GP. The highest response rates (CR + PR rates) were also observed in the GC-treated patients (52.4%), followed by GCarbo/GDCarbo (51.1%), GP (39.3%) and MVAC/MEC (35.3%). The 1-year and 3-year overall survival (OS) rates of the 345 patients were 47.0 and 16.6%, respectively. The 3-year OS of the patients treated with GC was 22.0%, which was the highest, followed by MVAC/MEC (16.0%), GCarbo/GDCarbo (14.0%), GP (5.2%) and other treatments (7.2%). Thus, the survival of the patients treated with GC was significantly better than that of the patients treated with the first-line chemotherapies other than GC (3-year OS: 22.0 vs. 14.4%, $P = 0.04$).

Since GC was the most frequently used first-line chemotherapy, we further analyzed the oncological outcomes of the GC-treated patients. Figure 2A provides the survival curve of all patients treated with GC. When stratified by renal function, as shown in Figure 2B, the survival of the patients with eGFR <60 ml/min/1.73 m^2 tended to be worse compared with that of the patients with eGFR ≥60 ml/min/1.73 m^2. The 3-year OSs were 14.1 and 31.4%, respectively, which was not a significant difference ($P = 0.075$). However, it is noteworthy that the dose reduction rate of the GC-treated patients with eGFR <60 ml/min/1.73 m^2 was high, at 43.9%. When limited to patients treated with a reduced dose of GC, the response rate tended to be low, at 29.6%. Additionally, the 1-year OS of the patients treated with a reduced dose of GC was significantly lower than that of the patients treated with the standard dose of GC (26.2 vs. 60.3%, respectively, $P = 0.0108$). Interestingly, there was no significant difference in survival curves between patients treated with a reduced dose of GC and the patients treated with GCarbo/GDCarbo. In the latter cases, the 1-year OS was 43.6%.

To identify the prognostic factors, we tested the seven prognostic variables listed in Table 3. When we examined the data in a univariate analyses, we found that dose reduction, metastases, PS and the chemotherapy regimens (GC vs. other than GC) were significant prognostic factors for OS. On the basis of the results of the univariate analysis, we performed a multivariate analysis using those four variables. As shown in Table 4, dose reduction, the presence of visceral metastases and PS were independent prognostic factors. Treatment with GC was not found to be a significant prognostic factor in the multivariate analyses.

Table 3. Univariate analyses of prognostic factors for overall survival

Category	No. of patients	3-year OS (%)	*P* value
Gender			
Male	245	18.5	0.8107
Female	100	11.8	
Age			
≥75 years	96	16.8	0.0809
<75 years	249	16.3	
Renal function			
eGFR ≥60 ml/min/1.73 m^2	145	19.8	0.219
eGFR <60 ml/min/1.73 m^2	200	14.6	
Dose reduction			
Yes	92	12.5	0.0063
No	253	18.2	
Chemotherapy			
GC	105	22.0	0.0413
Other than GC	240	13.9	
Metastasis			
None	21	48.0	<0.001
Lymph nodes	111	20.1	
Visceral	94	16.8	
Both lymph nodes and visceral	119	7.2	
Performance status (PS)			
0 or 1	323	17.0	0.0044
≥2	22	12.3	

Table 4. Multivariable analyses of prognostic factors for overall survival

Category	Hazard ratio (95% CI)	*P* value
Dose reduction		
No		0.0117
Yes	1.415 (1.082–1.834)	
Chemotherapy		
GC		0.0758
Other than GC	1.269 (0.976–1.668)	
Visceral metastases		
No		0.0002
Yes	1.583 (1.236–2.040)	
Performance status		
0 or 1		0.0165
≥2	1.889 (1.132–2.968)	

Discussion

The creatinine clearance rate (cCR) of 60 ml/min, measured by 24 h urine correction or estimated by the Cockcroft–Gault formula, has been the most widely used cutoff to judge the cisplatin eligibility of UC patients for chemotherapy. However, the eGFR has emerged as a more practical method to estimate renal function. After analyzing the present study of the delivery pattern and outcomes of chemotherapy according to eGFR values, we obtained several interesting findings.

First, when the eGFR cutoff level of 60 ml/min/1.73 m^2 was used for the definition of cisplatin eligibility, 58.0% of the 345 UC patients were defined as cisplatin-ineligible cases. The high cisplatin-ineligible rate was due in part to the relatively older ages of the patient population. The median age of the patients was 70 years. This is clearly older

than the subjects in the above-cited RCT comparing GC and MVAC (2); the median age in that study was 63 years. The younger population of the RCT is probably due to the entry criteria, in which a measured cCR of ≥60 ml/min was required. However, the age distribution of that RCT is not realistic in general practice. In unselected settings, several investigators reported the median age of advanced UC patients as ~70 years (16,17). In those populations, the authors reported similar high cisplatin-ineligibility rates of 33 and 46% in bladder cancer patients when they used the eGFR cutoff level of 60 ml/min/1.73 m^2 (16,17). The observed high cisplatin-ineligibility rate in the present study and others indicate that the assessment and management of renal impairment is essential in the general practice of chemotherapy for UC.

Second, as shown in Figure 1A, 128 (62.0%) of the 200 patients with eGFR values <60 ml/min/1.73 m^2 were treated with MVAC/MEC (33.5%) or GC (28.5%). It is of note that 46.3% of the patients with eGFR values <60 ml/min/1.73 m^2 were initially treated with GC since the introduction of gemcitabine in 2008 (Fig. 1C). Because of the retrospective nature of this study, the physicians involved made their treatment decisions based on the patients' 24 h cCR, the Cockcroft–Gault formula, serum creatinine level, eGFR or factors other than renal function such as PS. Nevertheless, the treatment procedure significantly differed below the eGFR cutoff level of 60 ml/min/1.73 m^2. The dose reduction rate was significantly higher in the patients with eGFR <60 ml/min/1.73 m^2 compared with those with eGFR ≥60 ml/min/1.73 m^2 (39.0 and 9.7%, respectively, $P < 0.001$).

Third, our multivariate analysis revealed that dose reduction was an independent unfavorable prognostic factor, as were visceral metastases and lower PS. Generally, it is known that lower dose intensity can be associated with unfavorable oncological outcomes. Our finding is thus not novel, but it is important in planning chemotherapy for patients with renal impairment in general practice. It is of note that a dose reduction can significantly affect the oncological outcome of patients treated with GC, which our analysis showed was the most frequently selected first-line chemotherapy after 2008. Overall, GC demonstrated the highest response rates and 3-year OS rate among the regimens examined here. The 3-year OS of the patients treated with GC was significantly better than that of the patients treated with a first-line chemotherapy other than GC (22.0 vs. 14.4%, $P = 0.04$). However, when patients were treated with GC, the survival of the patients with eGFR values <60 ml/min/1.73 m^2 tended to be worse compared with the patients with eGFR values ≥60 ml/min/1.73 m^2 (Fig. 2B).

Although multiple factors might be involved, dose reduction is considered to be a major responsible factor for poorer outcomes of GC treatment in patients with renal impairment. As shown in Figure 2C, the 1-year OS of the patients treated with reduced-dose GC was significantly lower that of the patients treated with the standard-dose GC (26.2 vs. 60.3%, respectively, $P = 0.0108$). These results suggest that alternative regimens might be optimal rather than reduced-dose GC in patients with eGFR values <60 ml/min/1.73 m^2.

In the present study, we did not observe any significant differences in the response rate or survival between the reduced-dose GC and GCarbo/GDCarbo groups. Several phase II studies of GCarbo as non-cisplatin first-line chemotherapy for patients with renal impairment have been reported (8–13), but the CR + PR rates were found to vary from 36 to 56%, largely depending on the patient's background and the dose intensity of carboplatin. However, the higher carboplatin dose was associated with higher hematological toxicities (9,11). The results of these studies suggest that GCarbo has some role in the treatment of UC patients with renal impairment, but the optimal regimen, especially the appropriate dose of carboplatin, remains unclear in the balance of efficacy and toxicity.

Although important findings were obtained in the present study, our analysis has several limitations. Many potential biases resulting from the retrospective design of the analysis must be taken into account. First, the number of delivered chemotherapy cycles might have affected the results. We observed that the response rates and OS in the patients treated with GC were better than those of the patients treated with MVAC/MEC, but the average number of chemotherapy cycles was 3.7 cycles in the GC group, which was significantly ($P < 0.0001$) higher than that of the MVAC group (2.6 cycles). Not only the difference in the number of treatment cycles but also the improvement of supportive care during the study period might have affected the oncological outcomes of both regimens. We thus speculate that the results presented here do not necessary show the superiority of GC compared with MVAC. Interestingly, when limited to the patients with eGFR <60 ml/min/1.73 m^2, the response rate of the patients who received four or more cycles of GC were significantly higher than that of the patients who received fewer than four cycles of GC. The response rates were 67.9 and 26.7%, respectively ($P = 0.0014$).

Second, the information on the treating physicians' decision-making process for the selection of first-line chemotherapy or for reduced-dose chemotherapy was not available. In addition, the method and timing of the response evaluations were different among the 17 institutions involved. Third, the present study focused on the delivery pattern of first-line chemotherapy. If progression was observed during or after the first-line chemotherapy, a significant proportion of the patients were supposed to receive second-line chemotherapy or radiotherapy. However, the present analysis lacked data about what type of treatment these patients received as second-line therapy. Unfortunately, precise data such as the date of progression and the reason(s) for terminating the first-line chemotherapy or changing the chemotherapy regimen were also not available. We were thus not able to analyze progression-free survival or the time to treatment failure in the present study.

Finally, we were not able to compare other equations, i.e. Cockcroft–Gault, measured cCR and others. Therefore, we cannot draw a conclusion regarding whether the eGFR cutoff level we used is reasonable or not for decision-making in chemotherapy. Despite the above-mentioned limitations, the size of the patient series and the multicenter contribution of unselected patients from 17 institutions allowed us to demonstrate that the eGFR cutoff level of 60 ml/min/1.73 m^2 is clinically meaningful in chemotherapy for UC.

In conclusion, in a large-scale retrospective study, we demonstrated that 58.0% of UC patients were defined as cisplatin-ineligible cases, using the eGFR cutoff level of 60 ml/min/1.73 m^2. In accord with previous studies, the present findings indicated that GC is the most preferred first-line chemotherapy for UC patients. However, in patients with eGFR values <60 ml/min/1.73 m^2, the superiority of GC compared with other regimens is apparently reduced. The results of the present study clearly demonstrate that the further development of standard treatments for patients with renal impairment is the most essential issue in chemotherapy for UC.

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Conflict of interest statement

None declared.

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Appendix

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