筑　波　大　学

博 士 （医 学） 学 位 論 文

Impact of acute kidney injury defined by CTCAE v4.0 during first course of cisplatin-based chemotherapy on treatment outcomes in advanced urothelial cancer patients.

（進行性尿路上皮癌の化学療法において
初回コース時の急性腎障害が予後に与える影響に
関する検討）

２０１９

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CONTENTS

ABSTRUCT

Introduction: To clarify the impact of acute kidney injury (AKI) during cisplatin-based chemotherapy on clinical outcome of patients with advanced urothelial cancer (UC).

Methods: I conducted a multicenter retrospective study including 230 UC patients who received gemcitabine and cisplatin (GC) or methotrexate, vinblastine, doxorubicin and cisplatin (MVAC). According to CTCAE v4.0, AKI was defined as an increase of serum creatinine (sCR) level of 0.3 mg/dL or more from baseline.

Results: The median age of patients was 67 yr. One hundred patients received GC; the remaining patients were treated with MVAC or MEC (methotrexate, epirubicin and cisplatin). During the first course of chemotherapy, AKI episodes were observed in 61 patients (26.5%). Pretreatment clinical factors including estimated glomerular filtration rate (eGFR) and creatinine clearance levels calculated using Cockcroft-Gault formula failed to identify a significant predictor for the development of AKI. AKI impacted renal function: at the start of second-course chemotherapy, the average eGFR of patients with AKI was 54.1 ml/min/1.73 m^2, significantly lower than that of patients without AKI (63.4 ml/min/1.73 m^2). As a result, only 57.4% of patients with AKI received the planned treatment at the second-course. Also, there was a significant difference between the AKI and no-AKI groups in the mean total chemotherapy cycles delivered (2.7 cycles and 3.3 cycles). Survival of patients who developed AKI was significantly worse than that of patients who did not. The 3-year OSs were 10.3% and 21.4%, respectively (P=0.02).

Conclusion: The present study demonstrated that AKI episodes during chemotherapy had a negative impact on both the intensity of subsequent chemotherapy and oncological outcomes.

INTRODUCTION

The vast majority of urothelial cancer (UC) is bladder cancer, accounting for about 95% of all urothelial cancer. This is followed by upper urinary tract cancer, renal pelvic cancer and ureteral cancer. Around 80% of bladder cancer patients are over 65 years old. In Japan, the age-adjusted morbidity and age-adjusted mortality are 6.8 and 2.1 per 100,000 persons-year, respectively (1). Probably due to ageing society, the morbidity increased to about 1.4 times compared to 15 years ago. Also, the mortality increased to 2.2 times (2).

The cisplatin-based combination chemotherapy is the standard management of metastatic urothelial cancer (UC). The chemotherapy also used as perisurgical treatment for local advanced UC. Today, gemcitabine and cisplatin (GC) is the most widely used first-line chemotherapy for UC (3), followed by methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) (4). One of the issues around cisplatin-based chemotherapy for UC is how to treat patients with renal impairment, because cisplatin, a key drug in both regimens, possesses nephrotoxicity. Although several mechanisms are involved, proximal tubular injury by necrosis or apoptosis is major pathophysiology of cisplatin-induced nephrotoxicity (5). It is known that the concentration of cisplatin in the proximal tubular epithelium is 5 time higher than serum concentration (6).

Generally, patients receiving cancer treatment are at increased risk for acute kidney injury (AKI). Recent population-based study reported that the overall cumulative incidence of AKI was high as 9.3% for patients initiating systemic therapy for cancer (7). Among various types of cancer, bladder cancer was associated with second highest 5-year AKI incidence (19%) next to multiple myeloma (26%). The authors also pointed out that pretreatment presence of chronic kidney disease (CKD) was associated with increased risk of AKI. In UC patients, recent investigations demonstrated the high prevalence of CKD (8, 9). Vaughn et al. reported that approximately 40 % of bladder cancer patients were judged to be cisplatin-ineligible due to renal impairment (10). Contrary to the high

prevalence of CKD, the impacts of pretreatment renal function and kidney injury during chemotherapy on clinical outcome are not well understood. We previously analyzed clinical outcomes of advanced UC patients grouped by first-line chemotherapy regimens and pretreatment renal function. In that multicenter retrospective cohort study including 345 UC patients, we found unsatisfactory oncological outcomes of GC for patients with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2(11). In this subgroup, dose reduction had a significant impact, and the 3-year overall survival (OS) of patients treated with reduced-dose GC at the first cycle was significantly lower than that of patients treated with the standard-dose GC (17.5% and 24.7%, respectively).

This finding suggests that additional renal impairment induced by chemotherapy also has an impact on clinical outcomes, because this common complication of cisplatin-based chemotherapy is often associated with suboptimal dose intensity in the subsequent treatment. Recently, acute kidney injury (AKI) was proposed as the new consensus term for acute renal failure. The diagnostic criteria for AKI proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) group are based on acute alterations in serum creatinine (sCR) or urine output (12). For the definition of AKI, the KDIGO criteria use an sCR ≥0.3 mg/dL increase within 48 hr or sCR ≥1.5× baseline occurring within the prior 7 days. This definition has been widely used in the fields of emergency medicine and surgery.

On the other hand, there is little information about the incidence or clinical significance of this moderate range of sCR increase during chemotherapy. In this context, the Common Toxicity Criteria for Adverse Events (CTCAE), which are widely used adverse-events criteria for chemotherapy, added ‘AKI’ as a new term in the latest version, CTCAE Version 4 (CTCAE v4.0). The CTCAE v4.0 also define AKI as an sCR exceeding 0.3 mg/dL, but with no description of a time course.

The previous multicenter patient cohort included 241 patients treated with GC or MVAC/MEC (methotrexate, epirubicin and cisplatin) as the first-line chemotherapy. I conducted the present retrospective study focused on development of AKI defined by CTCAE v4.0 during the first course of GC or MVAC/MEC to clarify pretreatment predictors for AKI, and to determine the impact of AKI on subsequent treatment and clinical outcomes.

MATERIAL AND METHODS

Study population

The present study enrolled 241 patients with advanced or unresectable UC who received GC or MVAC/MEC as first-line chemotherapy at 17 Japanese hospitals between January 2004 and December 2010. The patients who received perisurgical chemotherapy (neoadjuvant or adjuvant chemotherapy) or patients receiving chemoradiation for bladder preservation were excluded. All patients required pathological confirmation of UC, except patients with upper urinary tract cancer who were diagnosed by positive urinary cytology and radiological examinations.

The data at the start of chemotherapy included age, gender, TNM stage, site of metastases, status of kidney and sCR levels. The sCR levels measured during the first course chemotherapy were collected. Also, sCR levels prior to the start of the second course chemotherapy and sCR levels at the end of the first-line chemotherapy were collected. The planned dose of each drug, and the presence or absence of dose reduction were required for evaluating intensity of chemotherapy. The definition of dose reduction depended on each physician. Other information on the intensity of entire chemotherapy such as the number of cycles on first-line chemotherapy, the presence or absence of subsequent second-line or more chemotherapy, the regimen and number of cycles of

subsequent chemotherapy were also required. All data were collected from the medical records at each institution and registered by the secretariat server over the Internet. The data cleaning was performed with the cooperation of Tsukuba Clinical Research and Development Organization.

The eGFR was calculated using the formula reported by Matsuo et al. (13). This equation originated from the Modification of Diet in Renal Disease (MDRD) study group (14), and was adjusted for Japanese 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 creatinine clearance (CrCl) was calculated with the following Cockcroft-Gault formula: (140 – age) × body weight/plasma creatinine × 72 (× 0.85 for females) (15). This retrospective study was approved by the internal ethical committees of all participating institutions. IRB approval number was H23-33 in University of Tsukuba.

The follow-up statuses of patients were collected in December of 2013. The median follow-up duration was 10.9 mo (range: 1–97 mo).

Patient characteristics

In the present multicenter retrospective cohort study included 345 UC patients. Of them, 104 patients treated with non-cisplatin treatment were excluded from the study. Among the 241 patients enrolled, 10 patients were excluded due to missing data of sCR levels or kidney status. Another patient was excluded because he was undergoing hemodialysis. Backgrounds for the remaining 230 patients are presented in Table 1. The median age was 67 yrs (range: 35–85 yrs); those 75 years or older comprised 22.2%. Primary sites were the bladder in 120 patients (52.1%), upper urinary tract in 97 patients (42.2%) and both in 13 patients (5.7%). Approximately 94% of patients had metastatic disease at the start of chemotherapy. One hundred five patients had normal kidneys. The remaining 125 patients (54.3%) had some abnormality in the kidneys including

hydronephrosis (81 patients) and solitary kidney (44 patients). The median eGFR at the start of chemotherapy was 60.1 ml/min/1.73 m^2 (range: 25.9–133.7 ml/min/1.73 m^2). The median CrCl was 60.8 ml/min (range: 22.5-147.9 ml/min). One hundred patients (43.5%) received GC as initial chemotherapy; the remaining 130 patients (56.5%) were treated with MVAC (96 patients) or MEC (34 patients).

Evaluation of toxicity

The observed toxicities during the induction chemotherapy were graded according to CTCAE v4.0. To evaluate the incidence of AKI during chemotherapy, the highest sCR levels observed in each chemotherapy cycle were recorded. In CTCAE v4.0, grade 1 AKI was defined by an increase in sCR of 0.3 mg/dL or more or a 1.5-fold or more increase from baseline. Grade 2 was defined by sCR ≥2-fold increase and grade 3 AKI was sCR ≥3-fold increase from baseline or an increase in sCR of 4.0mg/dL. In the present study, I defined the baseline sCR level as the sCR of each patient just prior to the start of chemotherapy.

Statistical Analysis

Survival curves were constructed by the Kaplan–Meier method and compared using the generalized Wilcoxon test. The significance of differences of eGFR was assessed by Wilcoxon rank sum test and Chi-square test. The chi-square test was also used to compare response rates and to evaluate the association between variables and the occurrence of AKI. The log-rank test was used for comparison of survival between patient groups. The level of significance was set at $P < 0.05$. Statistical analysis was performed using Jmp®9 software (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Elevation of sCR during the first-course chemotherapy

During the first-course of chemotherapy, AKI with an sCR increase ≥0.3 mg/dL from baseline levels was observed in 61 patients (26.5%). AKI was observed in 40 of 130

patients (30.8%) receiving MVAC/MEC, a somewhat higher incidence than that during GC (21.0%), but the difference was not significant (P=0.10). Figure 1 illustrated the day which the highest sCR level was observed in each patient developed AKI. The highest sCR levels were observed at days 8–14 of the chemotherapy cycle in 37 patients (61.6%). This was followed by peak increases at days 1–7 in 13 patients (21.7%), days 15–21 in 7 patients (11.7%), and days 22–28 in 3 patients (5.0%). In 61 patients, the median increase of sCR was 0.47 mg/dL (range 0.3 to 1.8 mg/dL). Fifty-six of 61 patients (91.8%) were defined as grade 1 AKI. Grade 2 and grade 3 AKI were observed in 4 patients (6.6%) and one patient (1.6%), respectively. The sCR levels returned to baseline levels before the start of the second-course chemotherapy in 14 patients (26.9%). As summarized in Table 2, toxicities other than AKI during first-course chemotherapy were mainly myelosuppression. Grade 3/4 leukopenia, thrombocytopenia and anemia were observed in 55%, 27% and 14% of patients. The incidences of grade 3/4 leukopenia in patients with and without AKI were 65% and 51%, respectively. The difference was not significant (P=0.1). Also, there were no significant differences in the incidences of other toxicities between patients with and without AKI.

As shown in Figure 2A, development of AKI during first-course chemotherapy had an impact on subsequent renal function. The average eGFR at the start of second-course chemotherapy of patients with AKI was 54.1 ml/min/1.73 m^2, which was significantly lower than the eGFR of patients without AKI (63.4 ml/min/1.73 m^2, P<0.01). At this point, as shown in Figure 2B, patients with eGFR<60 ml/min/1.73 m^2 comprised 36 of 52 (69.2%) of the AKI group and 72 of 149 (48.3%) in no AKI groups (P<0.01). A significant difference was also observed in eGFR after the last course of GC or MVAC/MEC (54.35 ml/min/1.73 m^2 and 65.64 ml/min/1.73 m^2, respectively) (P<0.01). After GC or MVAC/MEC, eGFR<60 ml/min/1.73 m^2 was found in 44 of 60 (73.3%) patients and 75 of 165 (45.5%) in the no-AKI group (P<0.001). In the former group, 24

patients (54.5%) had eGFR of 45–59 ml/min/1.73 m^2, and 18 patients (40.9%) had eGFR of 30–44 ml/min/1.73 m^2.

Pretreatment predictors for development of AKI during the first-course chemotherapy

As shown in Table 3, I extensively analyzed pretreatment clinical factors as predictors for development of AKI with an sCR increase ≥0.3 mg/dL, including patient age, sex, primary tumor site, presence of visceral metastases, PS, dose reduction at the first-course chemotherapy eGFR and CrCl. But, there were no significant pretreatment predictors for development of AKI. The incidence of AKI in patients with eGFR<60 ml/min/1.73 m^2 and ≥ 60ml/min/1.73 m^2 were 32.2% and 20.9%, respectively. The incidence was somewhat higher in the former group, but the difference was not significant (P=0.07). Also, there was no significant difference in the incidences of AKI between patients with CrCl<60 ml/min and patients with CrCl≥60 ml/min (28.2% and 25.0%, respectively). I also performed the same analyses using different cut-off levels (55 and 50 ml/min/1.73 m^2 for eGFR and 55 and 50 ml/min for CrCl), but failed to find significant predictors for the development of AKI.

Impact of sCR elevation on intensity of subsequent treatment and clinical outcomes

I compared the intensity of subsequent chemotherapy delivered to patients having or not having AKI during first-course chemotherapy. As shown in Table 4, 127 of 169 patients (75.2%) without AKI received second-course chemotherapy with the planned regimen and dose. In contrast, only 35 of 61 (57.4%) patients received the planned treatment at the second-course. In the remaining 26 patients, 9 patients were treated with the same regimen with dose reduction, 8 patients received non-cisplatin-based chemotherapy, and 9 patients discontinued chemotherapy.

The development of AKI had an impact not only on the second-course chemotherapy but also on the intensity of the total chemotherapy. Fifty of 61 patients with AKI (82.0%) were treated with fewer than 4 cycles of chemotherapy; the proportion was significantly higher than that of patients without AKI (61.0%, P<0.01). Also, there was significant difference in the mean number of total chemotherapy cycles between the 2 groups (2.7 cycles and 3.3 cycles, P<0.01).

To identify the prognostic factors for OS, I tested 10 prognostic variables listed in Table 5. When examined by univariate analyses, visceral metastases, dose reduction at the first-course and grade3/4 leukopenia during first-course were significant prognostic factors for OS. The patients with pretreatment eGFR< 60 ml/min/1.73 m^2 and those with CrCl<60 ml/min showed lower OS compared to the control group, but the differences were not significant. In contrast, development of AKI during first-course chemotherapy had a significant impact on OS. Figure 3A represents the survival curve of patients stratified by presence or absence of AKI during first-course chemotherapy. The survival of patients who developed AKI was significantly worse than that of patients who did not develop AKI. The 3-year OSs were 10.3% and 21.4%, respectively (P=0.02). Figure 3B also showed the survival of patients stratified by presence or absence of AKI within 14 days after the start of chemotherapy. Again, patients developed AKI within 14 days had significantly worse prognosis compared patients did not develop AKI within 14 days. The 3-year OSs were 8.0% and 21.7%, respectively (P=0.03).

DISCUSSION

AKI has recently emerged as a new concept for acute renal failure. In the KDIGO criteria, AKI is defined by an increase in sCR ≥0.3 mg/dL or a ≥1.5-fold increase from baseline within 48 hr, which are rarely observed during chemotherapy. If the provision of

a time course for the sCR increase is not taken into account, nephrotoxicity with an sCR increase ≥0.3 mg/dL is often seen during chemotherapy for UC. Still, little is known about whether this moderate magnitude of sCR increase has an impact on the oncological outcomes of UC patients receiving cisplatin-based chemotherapy. The present study, in which I extensively analyzed delivery patterns and outcomes of chemotherapy among UC patients experiencing, revealed several novel findings.

First, the incidences of AKI during the first-course of GC and MVAC/MEC were 21.0% and 30.8%, respectively. To my knowledge, there are no other comparison data about the incidence of grade 1 AKI during first-course chemotherapy. A report of a large randomized trial comparing GC and MVAC did not describe the incidence of this moderate degree of sCR increase (3). One small study of GC in the adjuvant setting reported that an sCR increase up to >1.5 times the upper normal limit (UNL) was observed in 23% of patients(16). Sternberg et al reported the incidence of sCR>1.26– 2.5 × the UNL increase was 29% in 133 patients receiving MVAC (4). However, the reported incidences were observed during 2 to 6 courses of GC or MVAC, and were not restricted to first-course GC or MVAC. One Japanese study including 59 patients reported the incidence of sCR increase up to >1.5 × UNL was as low as 12% when limited to the first-course of MVAC (17).

The incidences of AKI reported here are higher than those in previous Japanese studies and those estimated from other studies (4, 16). This may be partly due to the older age of my patient cohort. The median age was 67 yrs, approximately 5 yrs older than that of patients enrolled in previous clinical studies (3, 4, 16). However, the age distribution in the present study is rather realistic in general practice. In unselected settings, several investigators have reported that the median age of advanced UC patients was around 70 yrs (18, 19). As shown in Table 3, extensive analysis including pretreatment eGFR and CrCl have failed to find an effective predictor for the development of AKI. Therefore,

assessment and management of AKI is essential in the general practice of chemotherapy for UC.

Second, as shown in Figure 2A and 2B, development of AKI in the first-course had a significant impact on subsequent renal function. When compared to patients with no AKI episodes, patients who developed AKI showed significantly lower eGFR at the start of the second-course chemotherapy. Consequently, the proportion of patients with eGFR<60 ml/min/1.73 m^2 was significantly higher in the AKI group compared to the no-AKI group (69.2% and 48.3%, respectively; P=0.01). Although multiple factors might be involved, it is likely that the difference of renal function between groups altered physician's decision making on the second-course chemotherapy. As shown in Table 4, in the AKI group, the proportion of patients who received the planned chemotherapy without dose reduction was significantly lower than that of patients in the no-AKI group (57.4% and 75.2%, respectively). A decrease in intensity of treatment of the former group was also found, with intensity defined as the total number of delivered chemotherapy sessions. In spite of chemotherapy with reduced intensity, it is of note that patients who developed AKI showed significantly lower eGFR after the last course of GC or MVAC/MEC. At this point, the proportion of patients with eGFR<60 ml/min/1.73 m^2 in the AKI and no-AKI groups were 73.3% and 45.5%, respectively (P<0.01). In the former group, 54.5% of patients had eGFR of 45–59 ml/min/1.73 m^2, and 40.9% of patients had eGFR of 30–44 ml/min/1.73 m^2. There is no doubt that second-line treatment (i.e. non-cisplatin-based chemotherapy or anti-PD-L1 treatment (20)) for these patients will become a matter of debate in the near future.

Third, to my interest, development of AKI during first-course chemotherapy had a significant impact on OS. As shown in Figure 3A, the 3-year OS values of the AKI and no-AKI groups were 10.3% and 21.4%, respectively (P=0.02). Univariate analyses during first-course chemotherapy showed that visceral metastases, dose reduction at the first-course and grade3/4 leukopenia during the first-course were significant prognostic factors

for OS. In contrast, the OS of patients with pretreatment eGFR<60 ml/min/1.73 m^2 and those with CrCl<60 ml/min tended to be worse than the control group, but without statistical significance. Recent investigations revealed that AKI is frequent in critically ill cancer patients or patients with metastatic disease (21, 22), and this combination can have a negative impact on many aspects of patient care (23). Therefore, multiple factors may be responsible for the observed worse prognosis of AKI patients in the present study. Nonetheless, my analysis demonstrated that the worse prognosis of patients who developed AKI in the first-course of chemotherapy was closely related to the lower intensity of the subsequent chemotherapy.

Although important findings were found, there are several limitations in my analysis. First, many potential biases resulting from the retrospective design of the analysis have to be considered. Information on the decision-making process for selecting subsequent chemotherapy was not available. Second, the present analysis lacks detailed data on the severity of comorbid medical diseases such as diabetes mellitus or hypertension. Such comorbidities associated with AKI (24) might indirectly affect outcomes. Finally, in the present study, I was not able to evaluate procedures to protect cisplatin-induced AKI such as aggressive hydration, mannitol and magnesium supplementation. Despite these limitations, the present large cohort of unselected patients from 17 institutions allowed me to demonstrate the importance of AKI during the first-course of GC or MVAC/MEC.

In conclusion, in this large retrospective study, I demonstrated that 26.5% of patients developed AKI during the first-course of GC or MVAC/MEC. The AKI episodes had negative impact on the intensity of subsequent chemotherapy and oncological outcomes. The results of the present study indicate that development of a standard renoprotective strategy and chemotherapy/targeted therapy for patients is the most essential issue for UC patients with renal impairment.

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ABBREVIATION & ACRONYMS

AKI= Acute kidney injury

AKIN= Acute Kidney Injury Network

CKD= Chronic kidney disease

CrCl= Creatinine clearance

CTCAEv4.0= Common Terminology Criteria for Adverse Events version 4.0

eGFR= estimated glomerular filtration rate

GC= Gemcitabine and cisplatin

IRB= Institutional Review Board

MDRD= Modification of Diet in Renal Disease

MEC= Methotrexate, epirubicin and cisplatin

MVAC= Methotrexate, vinblastine, doxorubicin and cisplatin

OS= Overall survival

PS= Performance status

sCR= Serum creatinine

UC= Urothelial cancer

SOURCE

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TABLE CAPTIONS

Table 1. Patient characteristics

Table 2. Adverse event during first-course chemotherapy

Table 3. Pretreatment clinical factors for development of acute kidney injury during first-course chemotherapy

Table 4. Performance of subsequent chemotherapy according to presence or absence of acute kidney injury during first-course chemotherapy

Table 5. Univariate analysis of prognostic factors for overall survival

FIGURE LEGENDS

Figure 1

The day each patient developed AKI

Figure 2

(A)Average eGFR after treatment according to presence or absence of acute kidney injury during first-course chemotherapy. P-value was assessed by Wilcoxon rank sum test (* not significant, **P<0.01).

a) Before the start of chemotherapy, b) Prior to the start of the second course of chemotherapy, c) After completion of the first-line chemotherapy

(B)Proportion of patients with eGFR>60, 45-60 and <45 ml/min/1.73 ㎡ according to presence or absence of acute kidney injury during first-course chemotherapy. P-value was assessed by Chi-square test (* not significant, **P<0.01, ***P<0.001).

a) Before the start of chemotherapy, b) Prior to the start of the second course of chemotherapy, c) After completion of the first-line chemotherapy.

The proportion of patients with eGFR<60 ml/min/1.73 m^2 was significantly higher in the AKI group compared to the no-AKI group (Prior to the start of the second course: 69.2% and 48.3%; P<0.01. After completion of the first-line chemotherapy: 73.3% and

45.5%, P<0.001)

Figure 3

Overall survival of patients according to presence or absence of acute kidney injury during first-course chemotherapy(A) and according to presence or absence of acute kidney injury within 14 days after the start of chemotherapy (B).

The survival of patients who developed AKI was significantly worse compared to patients who did not develop AKI. The 3-year OSs were 10.3% and 21.4%, respectively (P=0.02, Fig 3A). The prognosis of patients developed AKI within 14 days also significantly worse compared patients did not develop AKI within 14 days. The 3-year OSs were 8.0% and 21.7%, respectively (P=0.03, Fig 3B).

Table 1. Patient characteristics

Parameter	No.	%
All patients	230	
Age		
Mean (range), yrs	67 (35-85)	
Sex:		
Male	164	71
Female	66	29
Tumor location:		
Bladder	120	52
Upper urinary tract	97	42
Both bladder and upper urinary tract	13	6
Metastatic area:		
Lymph node	69	30
Visceral	69	30
Both lymph node and visceral	79	34
None	13	6
Performance status (PS):		
0 or 1	214	93
$\geq$2	16	7
Chemotherapy:		
GC	100	44
MVAC/MEC	130	56
Renal function:		
Mean creatinine (range), mg/dL	0.95 (0.38-2.07)	
Mean eGFR (range), ml/min/1.73 m^2	60.1 (25.9-133.7)	
Mean CrCl (range), ml/min	60.8 (22.5-147.9)	

eGFR, estimated glomerular filtration rate

CrCl, creatinine clearance calculated using Cockcroft-Gault formula

Table 2. Adverse events during the first-course chemotherapy

Acute kidney injury	All N=230	Presence n=61	Absence n=169	P-value
Adverse event (Grade 3/4):				
Leukopenia	126 (55%)	39 (65%)	87 (51%)	0.1
Neutropenia	18 (8%)	8 (13%)	10 (6%)	0.09
Thrombocytopenia	61 (27%)	16 (26%)	45 (26%)	1
Anemia	31 (14%)	11 (19%)	20 (12%)	0.27
Liver dysfunction	2 (1%)	0	2 (1%)	1

Table 3. Pretreatment clinical factors for development of acute kidney injury during first-course chemotherapy

Category	No. of patient	%	P-value
Age:			0.47
≥75 yrs	11/51	21.6	
<75 yrs	50/179	27.9	
Sex:			0.07
Male	49/164	30.3	
Female	12/66	18.2	
Tumor location:			0.30
Bladder	28/120	23.3	
Upper urinary tract or both bladder and upper urinary tract	33/110	30.0	
Visceral metastasis:			0.88
Yes	40/148	27.0	
No	21/82	25.6	
Performance status (PS):			0.25
0 or 1	59/214	27.6	
≥2	2/16	12.5	
Chemotherapy:			0.10
GC	21/100	21.0	
MVAC/MEC	40/130	30.8	
Dose reduction:			0.48
Yes	16/53	30.2	
No	45/177	25.4	
Kidney:			0.80
Normal	27/105	25.7	
Abnormal*	34/125	27.2	
eGFR:			0.07
≥60 ml/min/1.73 m^2	24/115	20.9	
<60 ml/min/1.73 m^2	37/115	32.2	
CrCl:			0.65
≥60 ml/min	30/120	25.0	
<60 ml/min	31/110	28.2	

*solitary kidney or hydronephrosis

Table 4. Performance of subsequent chemotherapy according to presence or absence of AKI during first-course chemotherapy

AKI (CTCAE v4.0)	Presence (n=61)	Absence (n=169)	
The second course chemotherapy	n (%)	n (%)	P-value
Planned treatment without dose reduction	35 (57.4)	127 (75.2)	0.01
Planned treatment with dose reduction	9 (14.7)	9 (5.3)	0.03
Other cisplatin-based chemotherapy	0 (0)	6 (3.6)	0.35
Non-cisplatin-based chemotherapy	8 (13.2)	7 (4.1)	0.03
No more chemotherapy	9 (14.7)	20 (11.8)	0.65
Total chemotherapy intensity			
Mean total treatment cycle (range)	2.7 (1–11)	3.3 (1–10)	<0.01
Less than 4 cycles	50 (82.0)	103 (61.0)	<0.01

Table 5. Univariate analysis of prognostic factors for overall survival (OS)

Category	No. of patients	3-years OS (%)	P-value
Tumor location:			0.06
Bladder	120	25.7	
Upper urinary tract or both bladder and upper urinary tract	110	10.7	
Visceral metastasis:			<0.01
Yes	148	13.8	
No	82	27.4	
Chemotherapy:			0.07
GC	100	21.5	
MVAC/MEC	130	15.9	
Dose reduction:			0.03
Yes	53	16.9	
No	177	18.6	
eGFR:			0.29
≥60 ml/min/1.73 m^2	115	22.1	
<60 ml/min/1.73 m^2	115	15.0	
CrCl:			0.88
≥60 ml/min	120	20.3	
<60 ml/min	110	16.1	
Kidney:			0.10
Abnormal	125	16.2	
Normal	105	19.8	
Acute kidney injury during first course:			0.02
Presence	61	10.8	
Absence	169	21.4	
Leukopenia during first course:			<0.01
<G3	103	23.2	
≥G3	126	15.1	
Thrombocytopenia during first course:			0.11
<G3	169	18.2	
≥G3	61	18.3	

Figure 1

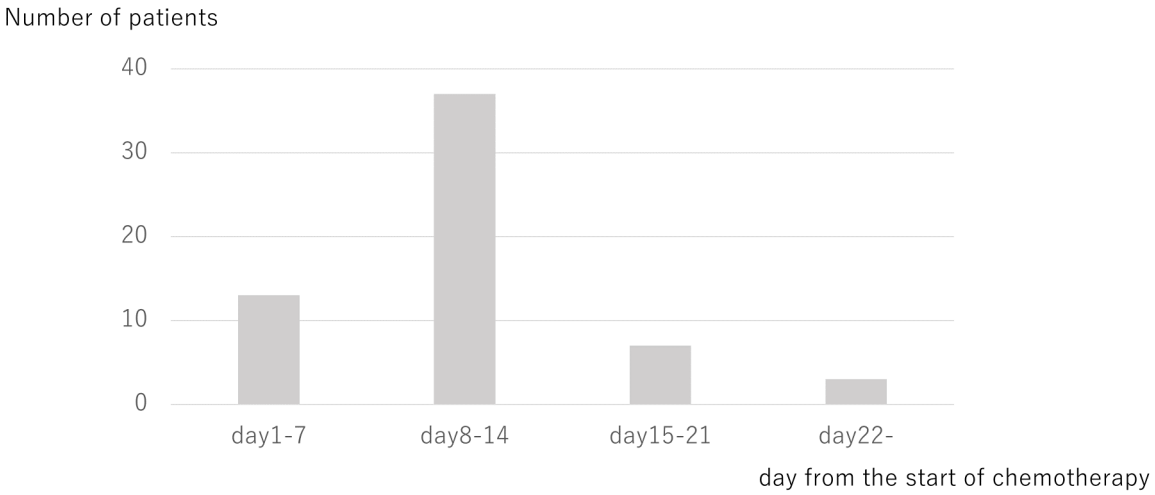

Number of patients
40
30
20
10
0
day1-7
day8-14
day15-21
day22-
day from the start of chemotherapy

Figure 2A

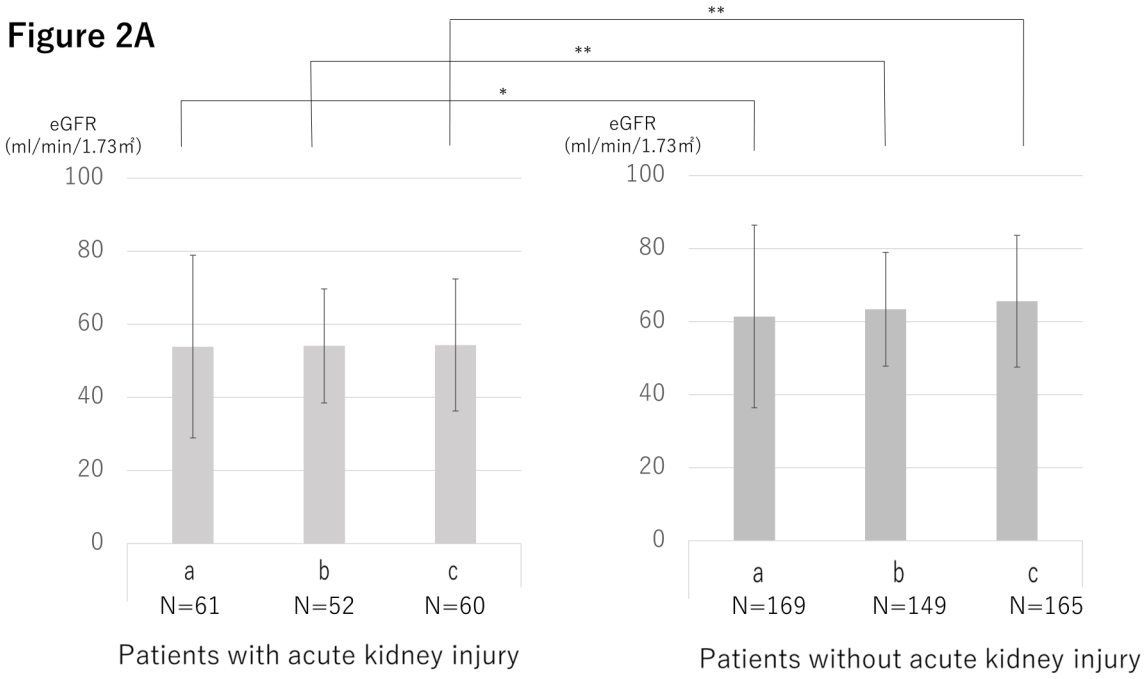

**
**
*
eGFR
(ml/min/1.73㎡)
100
80
60
40
20
0
a
b
c
N=61
N=52
N=60
Patients with acute kidney injury
eGFR
(ml/min/1.73㎡)
100
80
60
40
20
0
a
b
c
N=169
N=149
N=165
Patients without acute kidney injury

Figure 2B

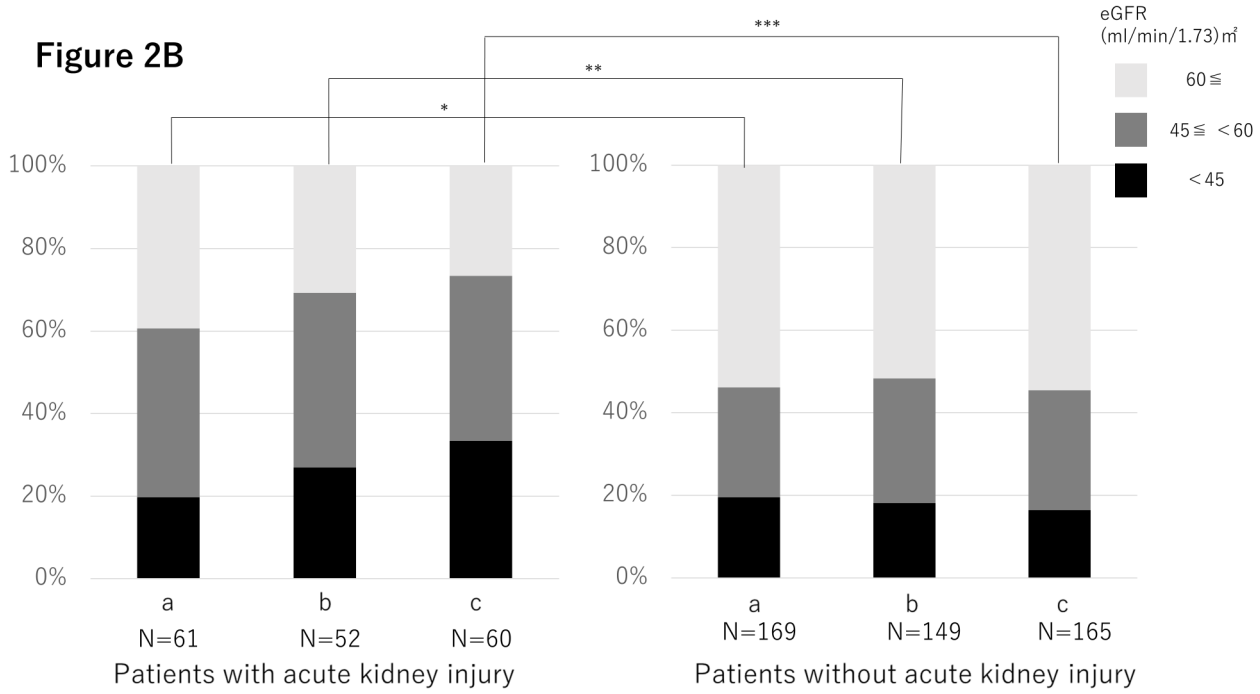

eGFR
(ml/min/1.73)㎡
60≦
45≦ ＜60
＜45
***
**
*
100%
80%
60%
40%
20%
0%
a
N=61
b
N=52
c
N=60
Patients with acute kidney injury
a
N=169
b
N=149
c
N=165
Patients without acute kidney injury

Figure 3A

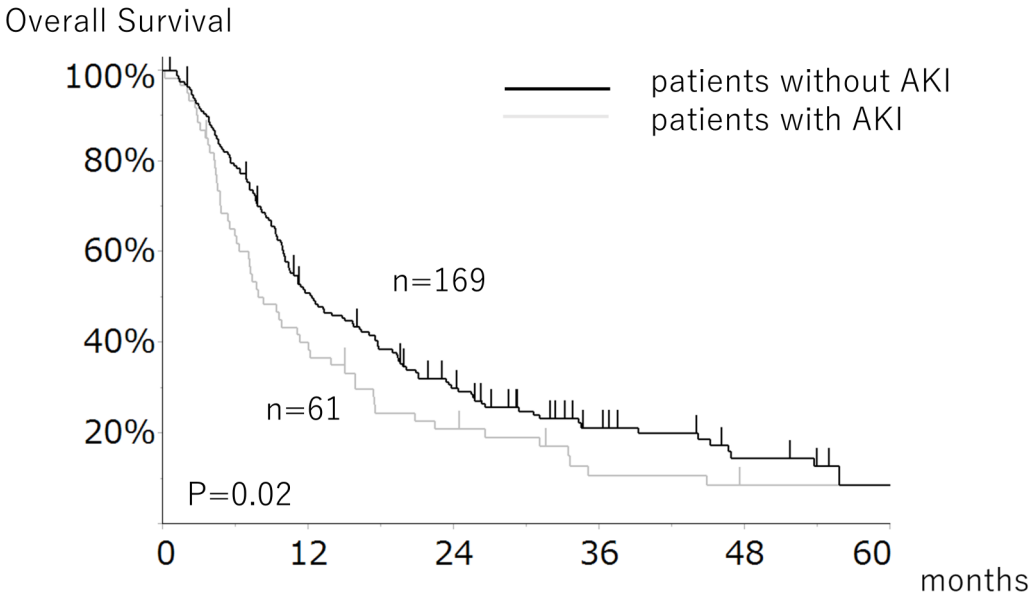
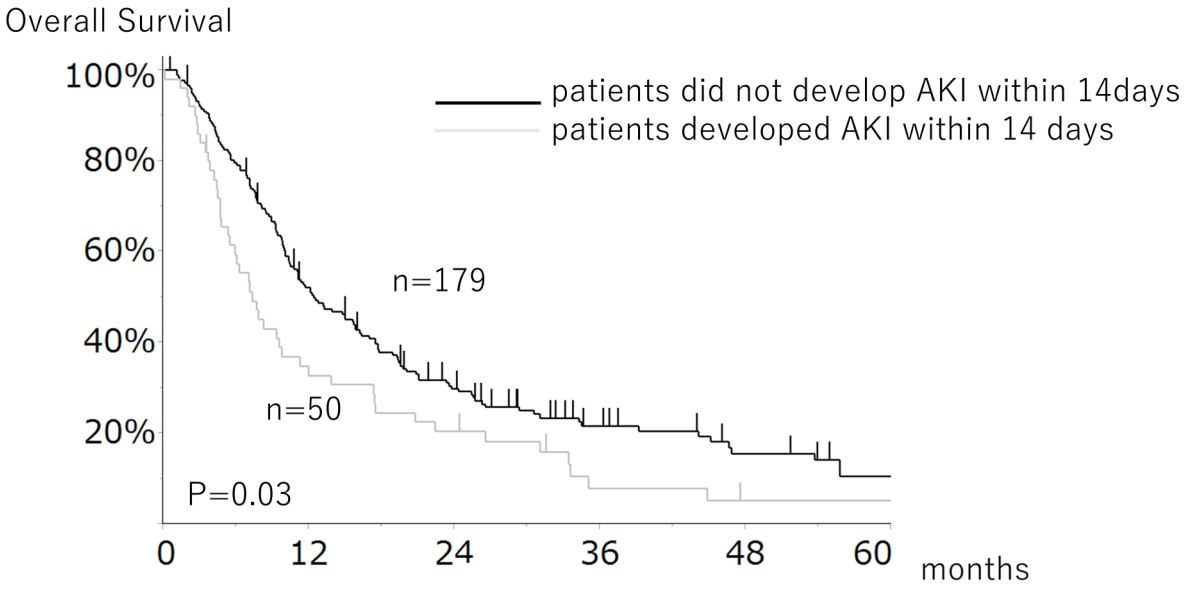

Overall Survival
100%
80%
60%
40%
20%
patients without AKI
patients with AKI
n=169
n=61
P=0.02
0
12
24
36
48
60
months

Figure 3B


Overall Survival
100%
80%
60%
40%
20%
patients did not develop AKI within 14days
patients developed AKI within 14 days
n=179
n=50
P=0.03
0
12
24
36
48
60
months