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ORIGINAL ARTICLE

Sarcopenia as a significant predictive factor of neutropenia and overall survival in urothelial carcinoma patients underwent gemcitabine and cisplatin or carboplatin

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Abstract

Background To evaluate the relationship between sarcopenia and myelosuppression or between sarcopenia and survival outcomes in patients with urothelial carcinoma (UC) undergoing chemotherapy with gemcitabine plus cisplatin (GC) or carboplatin (GCa).

Methods We evaluated 80 patients with UC who underwent chemotherapy between 2013 and 2017 at our institution. In total, 53 patients had metastatic UC and were ultimately included in the study. Predictive factors for myelosuppression (neutropenia, thrombocytopenia, and anemia) in all patients and overall survival (OS) in metastatic UC patients were analyzed. Sarcopenia was assessed on computed tomography before chemotherapy. Each patient's total psoas area was measured at the lumbar vertebrae (L3) and sarcopenia was defined as median values or lower. Predictive factors for myelosuppression were assessed using logistic regression analysis and survival was evaluated using Cox regression analysis.

Results The patients' mean age was 71.6 years (range 44.4–89.2 years). Of the initial 80 patients, 39 were diagnosed with sarcopenia and 26 of 53 patients with metastatic UC were diagnosed with sarcopenia. Sarcopenia was an independent predictive factor ($P=0.030$; odds ratio, 3.526; 95% confidence interval [CI] 1.128–11.01) for neutropenia on multivariate analysis. Patients without sarcopenia had a significantly longer OS compared to those with sarcopenia ($P=0.013$). Sarcopenia and albumin ($P=0.045$, 0.023; hazard ratio (HR), 2.309, 2.652; 95% CI 1.021–5.225, 1.141–6.165, respectively) were independent predictors of OS in multivariate analysis.

Conclusions Sarcopenia was predictive for neutropenia associated with GC or GCa in UC patients and OS in metastatic UC.

Keywords Urothelial carcinoma · Sarcopenia · Chemotherapy · Hematologic side effect · Overall survival

Introduction

In 1989, Rosenberg initially described sarcopenia as an age-related decrease in muscle mass [1]. In 2010, the European Working Group on Sarcopenia in Older People developed a clinical definition and reached a consensus regarding diagnostic criteria for age-related sarcopenia, indicating various causes for developing sarcopenia [2].

Recently, sarcopenia has been widely recognized by physicians and researchers for its potential in predicting various types of poor clinical outcomes. The association between sarcopenia and oncological convalescence has attracted attention and a study has reported that sarcopenia is a useful predictive factor of perioperative outcome and survival in melanoma, breast cancer, hepatocellular carcinoma, stomach cancer, and pancreatic cancer [3–7]. In urology, sarcopenia is associated with an increased risk of perioperative complications in urothelial carcinoma (UC) [8] and studies have described factors related to poor prognosis after radical cystectomy [9, 10]. Furthermore, sarcopenia is an independent predictive factor of poor convalescence in metastatic UC patients who have received chemotherapy [11, 12].

In Japan, approximately 20,000 patients are newly diagnosed with UC, resulting in 8000 deaths annually [13].

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First-line chemotherapy for advanced UC includes both a combination of gemcitabine and cisplatin (GC) and a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Long-term overall (OS) and progression-free survival (PFS) after GC or MVAC treatment are similar, but GC is preferred due to its lower toxicity [14], hence GC is administered to the majority of UC patients. However, patients with advanced UC are old, with impaired renal function due to age and disease. Therefore, we substitute gemcitabine and carboplatin (GCa) for GC in cisplatin-unfit patients. The prevalence of UC according to age increases in patients aged ≥ 60 years and decreases in those aged < 40 years [15]. According to recent studies, the prevalence of sarcopenia is relatively high, ranging from 15% at 65 years of age to 50% at 80 years of age [16]. In the present study, we investigated the influence of sarcopenia on the efficacy and side effects of GC (GCa) therapy and on PFS and OS.

Material and methods

Patients

We retrospectively reviewed 80 patients with UC who underwent first-line chemotherapy consisting of GC or GCa in our institution between April 2013 and February 2018. The majority of UC patients received gemcitabine 1000 mg/m^2 on days 1, 8, and 15 plus cisplatin 70 mg/m^2 on day 2; cisplatin-unfit patients (estimated glomerular filtration rate < 60 ml/min and Eastern Cooperative Oncology Group performance status (ECOG-PS) ≥ 2) received gemcitabine 1000 mg/m^2 on days 1, 8, and 15 plus carboplatin at an area under the curve of 5, according to the Calvert formula on day 2. Dose adjustment was permitted depending on the patient's general condition, creatinine clearance rate, and degree of bone marrow suppression. In total, 27 patients underwent radical cystectomy after chemotherapy and 53 underwent systemic chemotherapy. This study was approved by the Ethics Committee of Tottori University, Faculty of Medicine (approval number 18A038).

Variables evaluated were: age at first chemotherapy session, sex, ECOG-PS, T-stage, diabetes mellitus, smoking status, body mass index (BMI), body surface area (BSA), pretherapy C-reactive protein (CRP) level, pretherapy albumin level, the neutrophil-to-lymphocyte ratio (NLR), and cisplatin or carboplatin treatment.

Image analysis

All patients received computed tomography (CT) scans before chemotherapy to assess sarcopenia. The third lumbar vertebra (L3) was chosen as a landmark and sarcopenia was evaluated using a cross-sectional area of the bilateral psoas muscle, which was assessed using an OsiriX DICOM viewer. The cross-sectional area of the bilateral psoas muscles was normalized to the total psoas areas (TPA): bilateral psoas areas (cm^2)/body height (m^2). Due to differences in the TPA in male and female patients, a cutoff point was set for each sex. The median cutoff TPA was 4.57 cm^2/m^2 for males and 3.35 cm^2/m^2 for females.

Hematologic side effects

Hematologic side effects included neutropenia, thrombocytopenia, and anemia, which were assessed according to the common terminology criteria for adverse events, version 5.0. Adverse events were defined as grade ≥ 3.

Progression-free and overall survival for metastatic urothelial carcinoma patients underwent systemic chemotherapy

We evaluated the PFS and OS of patients who underwent systemic chemotherapy. Survival duration was defined as the interval between the day of initiating first chemotherapy course and the day of death.

Statistics

Patient characteristics and pretreatment factors were analyzed. Univariate and multivariate analyses and the calculation of odds ratios (ORs) were conducted using a logistic regression model. Survival curves were constructed using Kaplan–Meier analyses. The log-rank test was used to compare the survival between the patient groups; multivariate analysis was performed using a Cox regression model.

P values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS Statistics software version 15.0 (SPSS Inc.).

Results

Patients

Patient characteristics before chemotherapy are listed in Table 1. The mean age was 71.6 years (range 44.4–89.2 years). Of 80 patients, 53 (66%) had T4, lymph node metastasis or distant metastasis and underwent systemic chemotherapy without surgical treatment and 27 (34%) underwent neoadjuvant chemotherapy, followed by radical cystectomy for curative surgery. The median cutoff TPA for males and females was 4.57 and 3.35 cm^2/m^2, respectively. Overall, 39 of 80 patients had sarcopenia. In patients, with sarcopenia, albumin level, hemoglobin level,

Table 1 Patient characteristics before chemotherapy

	$n=80$
Age (years, mean range)	71.6 (44.4–88.2)
Sex *n*	
Male	55
Female	25
Performance status	
1≥	66
≥2	14
Tumor location	
Upper tract	23
Bladder	45
Both	12
T stage	
≥T3	59
T2≥	21
N stage	
≥1	41
0	39
M stage	
1	51
0	29
Diabetes mellitus	9
Smoking	
Yes	41
No	39
BMI (kg/m^2, mean range)	22.1 (13.3–30.7)
BSA (m^2, mean range	1.62 (1.17–2.28)
Alb (g/dL, mean range)	3.68 (2.3–4.6)
eGFR (mL/min, mean range)	59.0 (3.59–121.4)
CRP (mg/dL, mean range)	1.22 (0.02–15.11)
Type of platinum	
Cisplatin	29
Carboplatin	51

and BMI were significantly lower and CRP was significantly higher than those in patients without sarcopenia. Of patients with metastatic UC who underwent systemic chemotherapy, 27 had sarcopenia and 26 did not have sarcopenia.

Hematologic side effects

Neutropenia, thrombocytopenia, and anemia (grade ≥3) were observed in 61 (76%), 37 (46%), and 13 (16%) patients, respectively. Logistic regression analysis of hematologic side effects is shown in Table 2. In univariate analysis, CRP level and sarcopenia were candidates for the independent prognostic factors of neutropenia ($P=0.039$ and 0.025, respectively); in multivariate analysis, sarcopenia [$P=0.030$; OR, 3.526; 95% confidence interval (CI) 1.128–11.01] was an independent predictive factor of neutropenia. In univariate analysis, CRP and albumin were candidates for the independent prognostic factors ($P=0.048$ and 0.004, respectively) of thrombocytopenia; in multivariate analysis, albumin level ($P=0.004$; OR, 4.141; 95% CI 1.565–10.96) was an independent predictive factor of thrombocytopenia. In univariate analysis, CRP level, albumin level, and carboplatin treatment were candidates for the independent prognostic factors of anemia ($P=0.026$, 0.002, and 0.019, respectively); in multivariate analysis, albumin ($P=0.006$; OR, 9.240; 95% CI 1.892–45.13) was an independent predictive factor of anemia.

Best response, progression-free survival, and overall survival of patients with metastatic UC who underwent systemic chemotherapy

Among patients with metastatic UC who underwent systemic chemotherapy, 43 had complete response (CR), partial response (PR), and stable disease (SD) and ten had progressive disease (PD) for best response. Moreover, 20 patients with sarcopenia had CR, PR, and SD and 23 patients with no sarcopenia had CR, PR, and SD and the differences were not significant ($P=0.406$).

Figure 1a shows Kaplan–Meier survival curves for PFS in patients with sarcopenia and no sarcopenia in metastatic UC. There was no significant difference between the two groups ($P=0.667$).

Figure 1b shows Kaplan–Meier survival curves for OS in patients with sarcopenia and no sarcopenia in metastatic UC. Patients without sarcopenia had significantly longer OS compared to those with sarcopenia ($P=0.013$). Table 3 shows the results of Cox regression analysis for OS. CRP, albumin, and sarcopenia were candidates for the independent prognostic factors of OS ($P=0.007$, 0.006, and 0.013, respectively) in univariate analysis; albumin ($P=0.023$; HR, 2.652; 95% CI 1.141–6.165) and sarcopenia ($P=0.045$; HR, 2.309; 95% CI 1.021–5.225) were the independent predictive factors of OS in multivariate analysis.

Discussion

In 1989, Rosenberg et al. proposed the term "sarcopenia" (Greek: "sarx" or flesh + "penia" or loss) to describe the age-related decrease of muscle mass. Sarcopenia can be considered "primary", when no other cause is evident but aging and "secondary", when ≥1 other causes are evident. Secondary sarcopenia can be related to activity, disease, or nutrition [1]. Recently, sarcopenia has been recognized as a predictive factor of oncological outcome. However, currently, there is no clear definition of sarcopenia. Moreover, sarcopenia can be assessed using several techniques that include evaluating muscle mass, muscle length, and physical performance.

Table 2 Univariate and multivariate logistic regression analysis of hematologic side effects

	Univariate	Multivariate		
	P value	*P* value	95% CI	Odds ratio
Neutropenia				
Age (years: > 75 vs 75 ≥)	0.102			
Sex (male vs female)	0.272			
ECOG PS (>1 vs 1 ≥)	0.247			
BMI (kg/m^2: > 22 vs 22 ≥)	0.698			
BSA (m^2: > 1.6 vs 1.6 ≥)	0.221			
CRP (mg/dL: > 1.22 vs 1.22 ≥)	0.039	0.109		
Alb (g/dL: 3.68 > vs 3.68 ≥)	0.413			
NLR (3.47 > vs 3.47 ≥)	0.922			
Cisplatin vs carboplatin	0.089			
Dose	0.648			
Sarcopenia	0.025	0.03	1.128–11.017	3.526
Thrombocytopenia				
Age (years: > 75 vs 75 ≥)	0.137			
Sex (male vs female)	0.215			
ECOG PS (>1 vs 1 ≥)	0.779			
BMI (kg/m^2: > 22 vs 22 ≥)	0.642			
BSA (m^2: > 1.6 vs 1.6 ≥)	0.713			
CRP (mg/dL: > 1.22 vs 1.22 ≥)	0.048	0.73		
Alb (g/dL: 3.68 > vs 3.68 ≥)	0.004	0.004	1.565–10.96	4.141
NLR (3.47 > vs 3.47 ≥)	0.344			
Cisplatin vs carboplatin	0.51			
Dose	0.359			
Sarcopenia	0.642			
Anemia				
Age (years: > 75 vs 75 ≥)	0.748			
Sex (male vs female)	0.487			
ECOG PS (>1 vs 1 ≥)	0.826			
BMI (kg/m^2: > 22 vs 22 ≥)	0.838			
BSA (m^2: > 1.6 vs 1.6 ≥)	0.423			
CRP (mg/dL: > 1.22 vs 1.22 ≥)	0.026	0.467		
Alb (g/dL: 3.68 > vs 3.68 ≥)	0.002	0.006	1.892–45.125	9.24
NLR (3.47 > vs 3.47 ≥)	0.073			
Cisplatin vs carboplatin	0.019	0.054		
Dose	0.773			
Sarcopenia	0.106			

Muscle mass measurement is assessed using CT, magnetic resonance imaging, dual-energy X-ray absorptiometry, and bioimpedance analysis; muscle length is evaluated as a measure of handgrip strength, knee flexion/extension, and peak expiratory flow; and physical performance is measured using the Short Physical Performance Battery and usual gait speed, Timed Up and Go, and Stair Climb Power tests [2]. Furthermore, the cutoff values of various indices used to diagnose sarcopenia differ in the reported literature. The cutoff value for L3 skeletal muscle index (SMI) was 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women; patients below these values were classified as having sarcopenia [4, 5, 10, 12, 17–19]. Other studies have reported that sarcopenia is defined as SMI < 43 cm^2/m^2 for men with BMI < 25 kg/m^2, SMI < 53 cm^2/m^2 for men with BMI ≥ 25 kg/m^2, and SMI < 41 cm^2/m^2 for women [20–27]. Furthermore, Cheng-Le Zh et al. have reported that the sex-specific cutoff values of L3 SMI obtained by optimum stratification were 34.9 cm^2/m^2 for women and 40.8 cm^2/m^2 for men [6]. The cutoff values of TPA were defined by the ROC and AUC [9], the median TPA values for males and females [11, 12], and the presence of TPA in the lowest sex-specific quartile [17]. Thus, a standardized definition of sarcopenia that is suitable for use in research and clinical practice is still lacking [1,

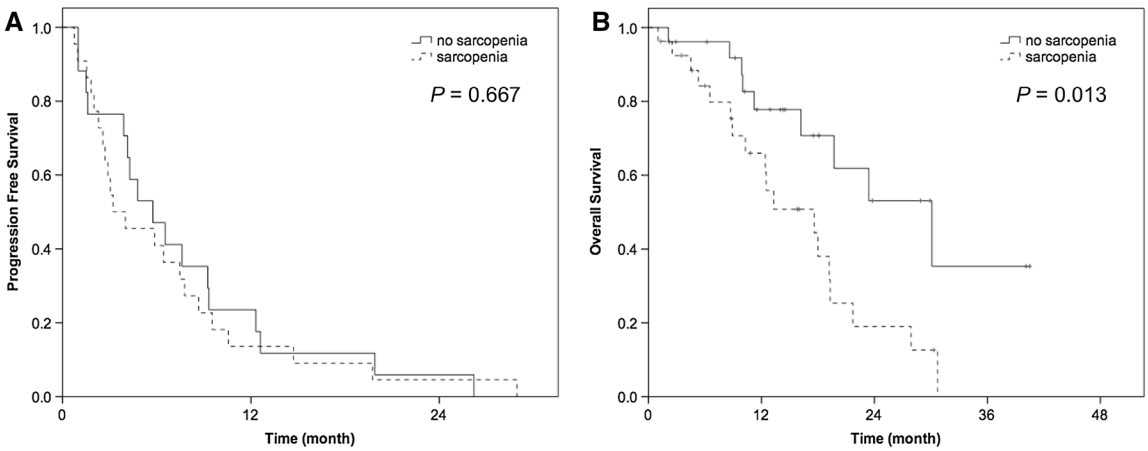

Fig. 1 **a** Progression-free survival in metastatic UC; **b** overall survival in metastatic UC

Table 3 Univariate and multivariate Cox regression models predicting overall survival

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years: > 75 vs 75 ≥)	1.544	0.687–3.471	0.293			
Sex (male vs female)	1.644	0.680–3.973	0.269			
ECOG-PS (>1 vs 1 ≥)	1.53	0.873–2.682	0.138			
T stage (T3 or more vs T2 or less)	0.899	0.361–2.236	0.819			
BMI (kg/m^2: > 22 vs 22 ≥)	1.184	0.550–2.547	0.666			
Smoking	1.524	0.650–3.574	0.333			
DM	1.551	0.576–4.176	0.385			
CRP (mg/dL: > 0.5 vs 0.5 ≥)	4.031	1.600–10.154	0.007			0.297
Alb (g/dL: > 3.5 vs 3.5 ≥)	4.429	1.722–11.391	0.006	2.652	1.141–6.165	0.023
NLR (>3.5 vs 3.5 ≥)	1.736	0.793–3.801	0.163			
Type of platinum (cisplatin vs carboplatin)	1.216	0.507–2.915	0.662			
Dose (100% vs 100% >)	0.529	0.224–1.250	0.147			
Sarcopenia	2.661	1.190–5.951	0.013	2.309	1.021–5.225	0.045

2]. Therefore, in this study, we used TPA determined using pretherapy CT to define sarcopenia and investigated sarcopenia's influence on the efficacy and the side effects of GC (GCa) therapy and on PFS and OS.

Recently, many reports have been published on the relationship between sarcopenia and poor outcomes in many types of cancer. Sabel et al. concluded that sarcopenia was associated with decreased and distant DFS and a higher rate of surgical complications in melanoma [3]. Zhuang et al. reported that sarcopenia was an independent predictive factor of severe postoperative complications after radical gastrectomy and independently associated with OS and DFS for gastric cancer [6]. In patients with unresectable locally advanced esophageal cancer, Sato et al. reported that the rate of OS was significantly worse in the group with sarcopenia [20]. For bladder cancer, sarcopenia was a predictive factor for early complications, cancer-specific survival, and OS after radical cystectomy [8–10, 21, 22]. Previous studies on upper tract UC reported that sarcopenia predicted longer hospitalization, cancer recurrence, and survival outcome after radical nephroureterectomy and was associated with lymphovascular invasion on pathologic findings [23–25, 28]. Furthermore, sarcopenia was a predictor of OS in patients with metastatic UC who underwent systemic chemotherapy [11, 12, 17, 26]. The results of the present study were similar to the aforementioned studies. Our study included 53 patients with advanced UC who underwent systemic chemotherapy (27 patients with sarcopenia and 26 with no sarcopenia). Patients with no sarcopenia had significantly longer OS compared to those with sarcopenia. Furthermore, multivariate analysis revealed that sarcopenia was an independent predictive factor of OS in advanced UC.

Previous studies have reported on the relationship between sarcopenia and adverse events in patients undergoing chemotherapy. Tan et al. reported that sarcopenia is a significant predictor of dose-limiting toxicity in gastric

cancer patients, undergoing neoadjuvant chemotherapy and the results may increase the potential for assessing skeletal muscle mass on CT scans to predict toxicity and individualize chemotherapy dosing [18]. Furthermore, Mir et al. have highlighted the emerging role of sarcopenia assessment for improving predictors of sorafenib-related toxicities, opening the gates to individualized drug dosing in patients with advanced HCC, which warrants validation in further prospective studies, evaluating toxicity after drug dosing based on pretreatment evaluation of sarcopenia [5]. However, to the best of our knowledge, no studies have reported that sarcopenia was a predictor of adverse events among UC patients undergoing chemotherapy. The present study demonstrated that sarcopenia was significantly associated with neutropenia in multivariate analysis. To the best of our knowledge, this is the first study to report on sarcopenia as a predictor of neutropenia in patients with UC undergoing chemotherapy. The exact mechanism explaining this relationship remains unclear. One of the mechanisms is that current chemotherapy dosing regimens are commonly based on BSA calculation [29]; therefore, patients with low muscle mass may have received a relatively higher dose. Our data demonstrated that the pretherapy evaluation of sarcopenia may predict neutropenia and individualized dose modification, and thus prevent febrile neutropenia. Prospective studies should be conducted to assess whether normalizing chemotherapy dose based on muscle mass decreases drug-induced toxicities.

In Japan, GC is presently considered the gold standard chemotherapy for patients with metastatic UC and neoadjuvant chemotherapy is typically used for advanced UC patients with no metastasis. However, many patients are unfit for cisplatin. According to Garsky et al., approximately 30–50% of patients are ineligible for cisplatin [30]. Carboplatin-based regimens are typically used as an alternative to cisplatin combination chemotherapy in cisplatin-unfit patients [31]. Similarly, in the present study, we used carboplatin for patients in whom cisplatin could not be used. A randomized study comparing toxicity and assessing the efficacy of GC and GCa in patients with advanced UC reported that median time to progression was 8.3 months for GC and 7.7 months for GCa, and median survival was 12.8 months and 9.8 months for GC and GCa, respectively [31]. Overall, 51 patients in the present study were unfit for cisplatin and were administered GCa. However, the type of platinum was not associated with OS ($P=0.662$). In total, 29 (74%) of 39 patients with sarcopenia were cisplatin unfit and 22 (53%) of 41 patients with no sarcopenia were cisplatin unfit. More patients were unfit for cisplatin in the sarcopenia versus no sarcopenia group. Therefore, sarcopenia may be an indicator of cisplatin-unfit patients.

Our study has some limitations. First, this was a retrospective study. Second, we used TPA determined using pretherapy CT to define sarcopenia. Currently, there is no optimal evaluation method for sarcopenia, and a clear definition of sarcopenia has not been established. Therefore, future studies may be needed to accurately define sarcopenia. Third, this study was a single-center study with a small number of patients. Despite these limitations, we were able to draw some useful conclusions from our data.

In conclusion, evaluating sarcopenia using TPA significantly predicted neutropenia and independently predicted poor prognosis in patients with advanced UC, undergoing first-line systemic chemotherapy. Our findings might prevent febrile neutropenia and aid in treatment planning in the management of advanced UC patients. Further multi-center studies with larger populations are warranted to confirm these results.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The need for informed consent was waived because of the retrospective nature of the study.

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