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Incidence of proteinuria following gemcitabine administration is a likely sign of poor outcome for cancer patients

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Abstract

Objective: It is well known that gemcitabine (GEM) rarely causes thrombotic microangiopathy. However, the prevalence and clinical significance of incident proteinuria among cancer patients after GEM administration are not fully understood.

Methods: This longitudinal cohort study aimed to confirm the prevalence of incident proteinuria after GEM administration and investigate its association with mortality in cancer patients: 53 with pancreatic, six with biliary, and one with gallbladder cancer. Proteinuria was defined as a urine dipstick test result ≥1+ in at least two consecutive examinations within 6 months after GEM administration. To determine the factors related to incident proteinuria, we compared patient characteristics by the presence or absence of incident proteinuria. The cumulative mortality rate was estimated using the Kaplan–Meier method, with stratification into two groups by the presence or absence of incident proteinuria. Furthermore, a multivariate Cox proportional hazards regression model was used to calculate the hazard ratio (HR) and its 95% confidence interval (CI) for all-cause mortality after adjustment for age, sex, and clinical cancer stage.

Results: The mean follow-up period was 1.03 ± 0.5 years, and the prevalence of incident proteinuria was 23.4%. The proportion of patients with a performance status score ≥2 was higher among those with incident proteinuria (4.4% vs. 50.0%: p = 0.0002), as were the C-reactive protein level (0.9 ± 1.3 vs. 1.7 ± 0.8 mg/dL; p = 0.0024) and cumulative GEM dose (8,140 mg/m^2 vs. 11,604 mg/m^2; p = 0.0189). Cumulative mortality was significantly higher in patients with incident proteinuria than in those without it (41.3% vs. 85.7%; p = 0.0002). On multivariate Cox proportional hazards regression, incident proteinuria was significantly associated with mortality (HR, 3.52; 95% CI, 1.58–7.51; p = 0.0028).

Conclusions: Incident proteinuria may be a marker of poor prognosis in pancreatic, biliary, and gallbladder cancer patients who received GEM.

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Introduction

Proteinuria is an insidious sign of chronic kidney disease (CKD) and a risk factor of progression to end-stage renal disease (ESRD) [1-4]. It is also a well-known independent risk factor associated with all-cause mortality in the general population and in patients with various diseases [5-8]. We previously confirmed that proteinuria was significantly associated with the serum interleukin 6 (IL-6) level and that the cumulative mortality was significantly higher in proteinuric patients than in non-proteinuric patients, with a graded relationship between proteinuria severity and mortality in 46 non-Hodgkin lymphoma (NHL) patients [3]. Gemcitabine (GEM), which was approved by the US Food and Drug Administration (FDA) in 1996 for the treatment of patients with metastatic pancreatic cancer, is currently used to treat a wide range of malignancies through monotherapy or combination therapy. GEM monotherapy remains the reference regimen for advanced pancreatic cancer [9,10], as its combined use with other cytotoxic drugs has not shown a significant benefit. On the other hand, it is recognized that patients who received GEM rarely suffered thrombotic microangiopathy (TMA) at a frequency of 0.015–1.4% [11-13]. Although rare, TMA is severe and may be fatal. However, the proportion of incident proteinuria (in cases without TMA) after GEM administration and the association between incident proteinuria and mortality has not been clarified. Therefore, here we addressed the following clinical questions to confirm the clinical importance of incident proteinuria in cancer patients who received GEM: [1] prevalence of incident proteinuria and [2] relationship between incident proteinuria and mortality.

Patients and methods

This longitudinal cohort study was approved by the institutional review board of Tokyo Metropolitan Komagome Hospital (approval no. 2071) and conducted in accordance with the Declaration of Helsinki Principles on Human Experimentations. Informed consent was obtained from all patients. The electronic medical records of all patients were reviewed to determine risk factors for mortality. The inclusion and exclusion criteria of this study were as follows: initial treatment with GEM, GEM monotherapy, follow-up period ≥ 6 months, estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m2, and no proteinuria at enrollment (**Figure 1**). A total of 60 cancer patients (31 men; mean age, 67 ± 8 years) were enrolled in the study between 2008 and 2011. Incident proteinuria was defined as a urine dipstick test score ≥1+ in at least two consecutive examinations within 6 months after GEM administration. Clinical cancer stage was defined according to the TNM classification of malignant tumors published by the Union for International Cancer Control (7th edition) (I–IV). General patient condition was classified as 0–4 according to the performance status (PS) [14]. The cumulative dose of GEM per body surface area at 6 months after starting the study was evaluated. Hypertension (HT) was defined as a systolic blood pressure of 140 mmHg and/or a diastolic blood pressure of 90 mmHg or the use of antihypertensive agents. Diabetes mellitus (DM) was defined as a diagnosis of DM prior to baseline, an HbA1c level ≥6.5% and a casual plasma glucose level ≥200 mg/dL, or the use of oral anti-diabetic agents or insulin. TMA was defined as follows: hemolytic anemia, decreased platelet count, presence of schistocytosis, and elevated lactate dehydrogenase (LDH) level during the follow-up period. Because renal biopsy did not examine for these patients, biopsy-proven TMA findings were not obtained.

Measurements

All patients provided blood and urine samples in the fasting state in the morning. The urinary specimens were simultaneously measured in the first spot urine voided in the morning. Proteinuria was measured using a dipstick test. Blood cell count and routine laboratory data were assessed using an automated SF-3000 Sysmex (Hitachi, Tokyo, Japan). Serum creatinine (Cr) was measured using an enzymatic method (N-assay L Creatinine Kit; Nittobo Medical Co. Ltd., Tokyo, Japan). The eGFR was calculated based on the serum Cr concentration, using the following equation: GFR (mL/min/1.73 m^2) = 1.94 × Cr-1.094 × age-0.287 × 0.739 (if female), which was developed for Japanese individuals by the Japanese Society of Nephrology due to the inaccuracy of the modified modification of diet in renal disease equation for Asian people, including Japanese [15].

Statistical analysis

All data are expressed as mean ± standard deviation (SD), unless otherwise stated. The statistically significant intergroup differences in continuous and categorical measures were analyzed using the Mann-Whitney U test and the chi-square test, respectively. Paired differences between the baseline and the end of the study period in eGFR were analyzed using Student's paired t-test. The statistical association of time to mortality with incident proteinuria was analyzed using Kaplan-Meier analysis, whereas the log-rank test was used to analyze the differences between the curves. Cox proportional hazards analysis, adjusted for covariates including age, sex, and cancer disease severity, was used to calculate the hazard ratio (HR) and its 95% confidence interval (CI) for mortality. All statistical analyses were performed using JMP 11.0.2 (SAS Institute Japan, Tokyo, Japan). P-values < 0.05 were considered significant.

Results

Demographic and laboratory characteristics of study patients

The demographic and clinical characteristics of all participants are shown in **Table 1**. The mean follow-up period was 1.3 ± 0.5 years, whereas the mean age was 67 ± 8 years; 31 male patients (51.7%) were included. The study population included patients with pancreatic cancer (n = 53), biliary cancer (n = 6), and gallbladder cancer (n = 1). The proportion of patients with cancer disease grade ≥ 3 was 78.3% (47 patients), whereas the proportion of patients with PS ≥ 2 was 15.0% (n = 9). The prevalences of HT and DM were 33.3% (n = 20) and 45.0% (n = 27), respectively. The mean albumin, hemoglobin, and eGFR levels at enrollment were 3.7 ± 0.5 g/dL, 11.2 ± 1.8 g/dL, and 84.2 ± 16.5 mL/min/1.73 m2, respectively. The mean total bilirubin, LDH, and C-reactive protein (CRP) levels at enrollment were 0.8 ± 0.8 mg/dL, 193 ± 105 IU/L, and 1.1 ± 1.2 mg/dL, respectively. No patients developed TMA during the study period.

Distribution and related factors of incident proteinuria

During the study period, 14 patients (23.4%) developed incident proteinuria. Of them, 10 (16.7%) developed 1+, three (5.0%) developed 2+, and one (1.7%) developed 3+ disease. The mean values of eGFR from the start to the end of the study period were significantly decreased (84.2 ± 16.5 to 69.5 ± 16.7 mL/min/1.73 m2; p = <0.0001). To determine the factors related to incident proteinuria, we compared patient characteristics by the presence or absence of incident proteinuria (**Table 2**). In this comparison, the proportion of patients with a PS ≥ 2 (4.4% vs. 50.0%; p =

0.0002) and the mean CRP value (0.9 ± 1.3 vs. 1.7 ± 0.8 mg/dL: p = 0.0024) were significantly higher in patients with incident proteinuria than in those without it. Further, the cumulative dose of GEM was also greater in patients with incident proteinuria than in those without it (8,140 mg/m^2 vs. 11,604 mg/m^2;p = 0.0189).

Impact of incident proteinuria on time to mortality

Of the entire cohort, 31 (51.7%) died during the study period. The most common cause of death was cancer exacerbation. The Kaplan-Meier curve, stratified by the presence or absence of incident proteinuria, is shown in **Figure 2**. Cumulative mortality was significantly higher in patients with incident proteinuria (85.7% vs. 41.3%; p = 0.0002). In the multivariate Cox proportional hazards regression model, incident proteinuria was significantly associated with time to mortality compared to the absence of incident proteinuria (HR, 3.52; 95% CI, 1.58–7.51; p = 0.0028).

Discussion

This study showed that 14 patients (23.4%) developed incident proteinuria, an independent factor for mortality. Moreover, patients with incident proteinuria had a higher proportion of PS ≥ 2, CRP value, and cumulative dose of GEM than did those without proteinuria.

We showed that the prevalence of incident proteinuria was 23.4% and that the CRP value, PS ≥ 2, and cumulative dose of GEM were significantly greater in patients with incident proteinuria. Further, no patients developed TMA. There have been no clinical studies on the prevalence of incident proteinuria after GEM administration. On the other hand, several studies have shown the clinical significance of proteinuria in patients with cancer [3,16-18]. Sawyer et al. showed that the prevalence of proteinuria (defined as urinary proteinuria concentration > 0.1 g/L in spot urine) was significantly higher in patients with cancer than in those without cancer (7.3% vs. 34.5%) [19]. We also demonstrated that the prevalence of proteinuria (defined as a dipstick test result > 1+ on at least three consecutive examinations) was 15.2% in 46 NHL patients in a 1-year prospective cohort study [3]. This result was higher than that in the general population. So what causes proteinuria in these patients? We first demonstrated that the CRP level and proportion of patients with PS ≥ 2 were significantly higher in patients with incident proteinuria. Therefore, the presence of proteinuria may reflect hidden systemic inflammation, characterized by elevation of the CRP and serum IL-6 concentrations. It is well known that patients with cancer suffer from chronic inflammation, and the correlation between cancer and abnormal urine findings and renal dysfunction has been suggested in several clinical studies [20-24]. Meanwhile, we speculated that inflammation, which is associated with cancer, might cause renal tubular damage and vascular endothelial impairments resulting in incident proteinuria [25]. Second, the fact that the cumulative dose of GEM was greater in patients with incident proteinuria was notable. It is well recognized that GEM-associated TMA has a probability of 0.015–1.4% [11-13]. The risk for GEM-associated TMA appears to increase with a cumulative drug dose > 20,000 mg/m^2 or drug administration for >18 cycles [26]. In our study, the prevalence of incident proteinuria was high, although no patients developed TMA. The cumulative administration of GEM was 11,604 mg/m2 in patients with incident proteinuria, significantly greater than in those without it (8,140 mg/m^2). It is possible that, in some patients, particularly those with stable or expanding disease who continue to receive GEM, the cumulative effect of this glomerular endothelial damage may result in the development of incident proteinuria. Therefore, patients with prevalent incident proteinuria may reflect transient glomerular endothelial damage caused by GEM. According to these results, incident proteinuria might be caused by inflammation due to cancer and GEM administration in a dose-dependent manner. On the other hand, mean values of eGFR were significantly decreased during study period. Therefore, this may be a part of the causality of incident proteinuria though eGFR at the end of the study period were not advanced CKD level.

Patients with incident proteinuria may be at higher risk of mortality than those without it. In our study, 31 patients (51.7%) died during a mean follow-up of 1.3 ± 0.5 years. The cumulative mortality of patients with incident proteinuria contributed to a two-fold greater increase in cumulative mortality. In the Cox proportional hazards regression analysis, after adjustment for known risk factors, incident proteinuria was significantly associated with mortality (HR, 3.52; 95% CI, 1.58–7.51; p = 0.0028). Several studies have suggested that the prognosis of cancer patients is poor in the presence of proteinuria. Sawyer et al. showed that the prevalence of proteinuria was significantly higher in patients with cancer than in those without cancer and was associated with mortality in various cancers [19]. We demonstrated that the presence of proteinuria led to a significantly poor prognosis and that the HR for mortality increased markedly as urinary protein concentration increased [3]. These results are consistent with ours. On the other hand, the concrete reason for the strong association between incident proteinuria and mortality remains undetermined. Chronic inflammation may explain the association between incident proteinuria and oncological outcome [27]. In fact, patients with incident proteinuria had a higher mean CRP value and proportion of PS ≥ 2 as well as a greater cumulative dose of GEM. Considering these results, incident proteinuria may be a surrogate marker for systemic inflammation related to cancer, which may lead to refractory chemotherapy. Therefore, incident proteinuria after GEM administration may be a marker of mortality in patients with pancreatic, biliary, or gallbladder cancer.

The study has several limitations. First, it was undertaken on the basis of the fact that dipstick proteinuria could be utilized as a convenient alternative to albuminuria. Although albuminuria would be expected to be more accurate for evaluating kidney glomerular damage and prognosis than dipstick proteinuria, the test for albuminuria is more expensive and not readily applicable for users in a general clinical setting from the perspective of Japan's health insurance system. Moreover, the cause of incident proteinuria was not examined pathologically. However, a renal biopsy is generally unfeasible in patients with cancer, especially those undergoing chemotherapy, because of perceived risks. Second, because of the small sample size of patients who developed incident proteinuria, we could not perform a multivariate analysis of the relative factors of incident proteinuria. However, we obtained an interesting result, that is, the proportion of patients with PS ≥ 2, the mean CRP value, and the cumulative dose of GEM were significantly higher among patients with incident proteinuria. Further large study will be needed to confirm our results and to try and firmly elucidate the possible mechanisms. Third, variables such as treatment- and time-related factors and nutritional status were not considered as covariates in the multivariate Cox proportional hazard analyses.

Conclusion

In conclusion, incident proteinuria may be associated with systemic inflammation due to cancer and may be a marker of

poor prognosis in patients with pancreatic, biliary, or gallbladder cancer who received GEM.

Disclosure Statement

The authors declare no conflicts of interest.

Statement of Ethics

The appropriate ethics committee approved this study and all participants gave informed consent.

Figures

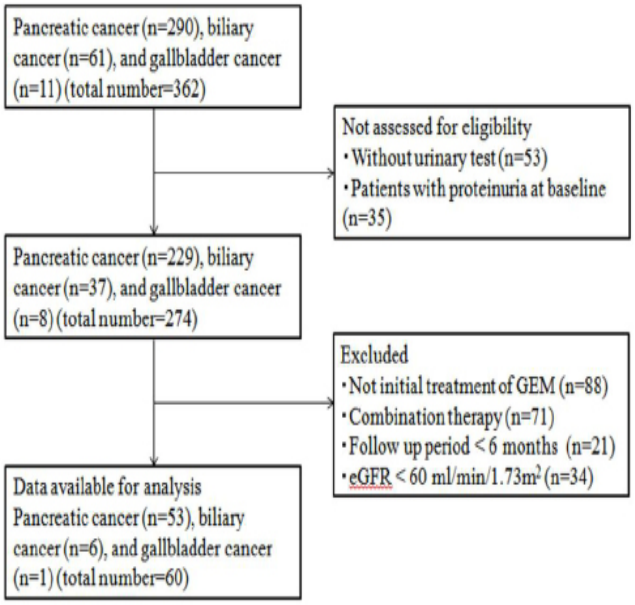

Figure 1: Flow diagram of the study

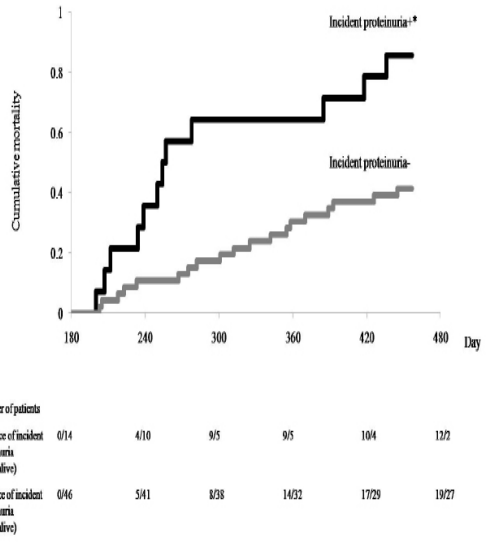

Figure 2: Cumulative curves of mortality were prepared using the Kaplan-Meier method, while the differences between curves were examined using the log rank test. The curves were drawn and stratified by the presence or absence of incident proteinuria. The asterisk (*) indicates a statistical significance versus the non-incident proteinuria patient group (reference).

Tables

Table 1: Demographic and laboratory characteristics of the study patients

Number of patients	60
Age (y)	67 ± 8
Men (%)	51.7
Performance status ≥ 2 (%)	15.0
Stage of disease ≥ 3 (%)	78.3
Hypertension (%)	33.3
Diabetes mellitus (%)	45.0
eGFR (mL/min/1.73 m²)	84.2 ± 16.5
Hb (g/dL)	11.2 ± 1.8
Alb (g/dL)	3.7 ± 0.5
T-bil (mg/dL)	0.8 ± 0.8
LDH (IU/L)	193 ± 105
CRP (mg/dL)	1.1 ± 1.2

Data are expressed as mean ± standard deviation.
Abbreviations: Alb: albumin; CRP: C reactive protein; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; LDH: lactate dehydrogenase; T-bil: total bilirubin

Table 2: Demographic and laboratory characteristics of the study patients

	Presence of incident proteinuria (n = 14)	Absence of incident proteinuria (n = 46)	P value
Age (y)	66 ± 9	68 ± 8	0.7198
Men (%)	64.3	47.8	0.3652
Performance status ≥ 2 (%)	50.0	4.4	0.0002
Stage of disease ≥ 3 (%)	85.7	76.1	0.7128
Hypertension (%)	21.4	37.0	0.3470
Diabetes mellitus (%)	50.0	43.5	0.7631
eGFR (mL/min/1.73 m²)	85.6 ± 18.3	83.9 ± 16.1	0.9791
Hb (g/dL)	10.4 ± 1.8	11.4 ± 1.8	0.0502
Alb (g/dL)	3.8 ± 0.1	3.7 ± 0.1	0.5694
T-bil (mg/dL)	0.9 ± 0.7	0.7 ± 0.7	0.0813
LDH (IU/L)	244 ± 27	178 ± 15	0.0950
CRP (mg/dL)	1.7 ± 0.8	0.9 ± 1.3	0.0024

Data are expressed as mean ± standard deviation.
Abbreviations: Alb: albumin; CRP: C reactive protein; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; LDH: lactate dehydrogenase; T-bil: total bilirubin

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