Toxicology 359–360 (2016) 71–75

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Early prediction of cisplatin-induced nephrotoxicity by urinary vanin-1 in patients with urothelial carcinoma

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ARTICLE INFO

Article history:
Received 27 May 2016
Accepted 14 June 2016
Available online 16 June 2016

Keywords:
Early biomaker
Renal function
Cisplatin
Urothelial carcinoma

ABSTRACT

Cisplatin is a widely used anticancer drug, but its nephrotoxicity is a serious problem. To examine whether the novel biomarker, urinary vanin-1, could predict reduction in renal function after dosing of cisplatin. We conducted a prospective single-center pilot study of 24 patients with urothelial carcinoma who received cisplatin-based chemotherapy between 2012 and 2015. The primary outcome was a 20% or greater decline in estimated glomerular filtration rate (eGFR) from baseline within the first 6 days of cisplatin. Urine concentration of creatinine, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and NAG (*N*-acetyl-β-D-glucosaminidase) as well as vanin-1 were measured during the perioperative period. During 6 days after cisplatin, 37.5% (9/24) of patients showed more than 20% decline in eGFR (baseline, 68.8 ± 11.1 mL/min/1.73 m^2; on day 6, 51.0 ± 2.5 mL/min/1.73 m^2) and this reduction persisted until day 10. Urinary vanin-1, but not KIM-1, NGAL and NAG, significantly elevated early on day 3 after cisplatin, which preceded the elevation of serum creatinine on day 6. Sensitivity and specificity of a cutoff point of urinary vanin-1 (9.31 ng/mg Cr) on day 3 were calculated to be 66.7% (95% CI: 0.30-0.93) and 83.3% (95% CI: 0.52-0.97), respectively, for predicting 20% decline in eGFR during 6 days after cisplatin. These data suggest that urinary vanin-1 is an early predictive biomarker for decline in eGFR in patients with urothelial carcinoma after dosing of cisplatin.

1. Introduction

Urothelial carcinoma (UC) is one of the most common cancers in the world, which occurs mainly in the elderly. UC is a chemosensitive disease with a relatively higher overall (50–70%) and complete (10–20%) response rates under cisplatin-based regimens (Logothetis et al., 1990; von der Maase et al., 2000). Although cisplatin has a strong anticancer effect, it causes several toxicities including nausea, neuropathy, myelosuppression and nephrotoxicity. Especially, nephrotoxicity is a serious problem; it sometimes leads to cessation or change of cisplatin-based chemotherapy in future cycle. Therefore, it is required to detect the cisplatin-induced nephrotoxicity at an earlier stage for therapeutic interventions.

The most frequently used biomarkers for renal damage are serum creatinine (Scr), blood urea nitrogen (BUN), and Cr clearance, all of which are insensitive and nonspecific for detection of renal injury (Star 1998). Recently, several new biomarkers for renal damage are identified. For example, the increased urinary excretions of kidney injury molecule-1 (Kim-1) (Ichimura et al., 1998; Vaidya et al., 2006; Han et al., 2002), neutrophil gelatinase-associated lipocalin (NGAL) (Mishra et al., 2003), (Mishra et al., 2004) and *N*-acetyl-β-D-glucosaminidase (NAG) (Westhuyzen et al., 2003) are shown to reflect proximal tubular damage. We also found that urinary excretion of vanin-1, which is an epithelial glycosylphosphatidylinositol (GPI)-anchored pantetheinase (Aurrand-Lions et al., 1996; Pitari et al., 2000) elevates before the urinary increases of Kim-1, NGAL and NAG in rats with the nephrotoxicant- and drug-induced renal tubular injury (Hosohata

Abbreviations: eGFR, estimated glomerular filtration rate; KIM-1, kidney injury molecule-1; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; GC, gemcitabine and cisplatin; MVAC, methotrexate, vinblastine, doxorubicin, adiamycin, and cisplatin; UC, urothelial carcinoma.

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http://dx.doi.org/10.1016/j.tox.2016.06.011
0300-483X/

et al., 2011; Hosohata et al., 2012). These data led us to speculate that compared to urinary Kim-1, NGAL and NAG, urinary vanin-1 is an earlier biomarker for renal tubular damage in patients with cisplatin-chemotherapy. This study was the first step to address the hypothesis. Time courses of eGFR and urinary excretions of vanin-1, Kim-1, NGAL and NAG were determined in UC patients after dosing of cisplatin.

2. Materials and methods

2.1. Patients and study design

The prospective observational study was approved by the Ethics Committee of Jichi Medical University (no. A11-47) and conducted between January 2012 and March 2015. UC adult patients who were scheduled to receive the cisplatin-based chemotherapy at our hospital were recruited. In total, 36 patients (30 men and 6 women) were participated after providing written informed consent. The following patients were excluded; in whom chemotherapy regimen was changed from cisplatin to carboplatin (n = 2), who did not collect urine samples (n = 1), who suffered bacterial infection which could affect urinary concentration of biomarkers (n = 7) and in whom renal function could not be controlled (n = 2) under MVAC (methotrexate, adriamycin, cisplatin and vinblastine instead of using gemcitabine) regimen. Thus, the study population consisted of 24 patients.

2.2. Diagnostic criteria for cisplatin-induced renal impairment

The GC regimen (1000 mg/m^2 of gemcitabine on days 1 and 8, and 70 mg/m^2 of cisplatin on day 1) were performed every 3 weeks. Patients were hydrated during the regimen using saline plus furosemide (Table 1). Blood biochemical tests were performed at least once a week in most patients. Because UC occurs largely in the elderly, we defined cisplatin-induced renal damage using the estimated glomerular filtration rate (eGFR) as follows: (1) a 20% or greater decrease in eGFR from baseline within the first 6 days after cisplatin, and (2) no obvious cause of decrease in eGFR other than cisplatin. The eGFR was calculated according to the equation for the Japanese: eGFR (mL/min/1.73 m^2) = $194 \times (\mathrm{Scr})^{-1.094} \times (\mathrm{Age})^{-0.287} \times (0.739$ if female) (Matsuo et al., 2009).

2.3. Urine collection and biomarker analysis

Morning urine samples were obtained before and on days 1, 3 and 6 after dosing of cisplatin. Cr and NAG was measured by an enzymatic method and a colorimetric method, respectively (SRL, Tokyo, Japan). The biomarker candidates were measured using commercially available ELISA kits (vanin-1, Cloud-Clone Corp, Houston, TX; KIM-1 and NGAL, R&D Systems, Minneapolis, MN), according to the manufacturer's instructions.

2.4. Statistical analyses

Variables between two groups were compared using the nonparametric Mann-Whitney *U*-test and chi-square test as appropriate. For time course studies, data were compared using two-way ANOVA followed by Bonferroni's *post hoc* analysis. The ability of biomarkers to discriminate between patients experiencing the primary outcome within 6 days after administration of cisplatin was determined using receiver-operating characteristic (ROC) curves, providing sensitivity and specificity with 95% confidence intervals (CI) to detect cisplatin-induced nephrotoxicity. Probability analysis was performed according to the Kaplan-Meier method, and the outcome was compared between the subgroups using a log-rank test. A value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed using GraphPad PRISM version 4 (GraphPad Software, Inc., San Diego, CA) and SPSS version 11 (SPSS Japan, Tokyo, Japan).

3. Results

3.1. Patients characteristics

A total of the 24 patients, median age was 70 years (range 46–84), 20 (83.3%) were men, 10 (41.7%) patients had G3 tumor grade, 17 (70.8%) had high pathological T stage (greater than T2), 8 (33.3%) showed positive lymph node metastasis, 6 (23.1%) had concomitant carcinoma in situ. All patients received cisplatin-based chemotherapy which consisted of GC (gemcitabine and cisplatin). During 6 days after cisplatin, 9 (37.5%) patients experienced 20% decline in eGFR (baseline, 68.8 ± 11.1 mL/min/1.73 m^2; on day 6, 51.0 ± 2.5 mL/min/1.73 m^2). As shown in Table 2, there were no significant differences in baseline variables including renal function and dose of cisplatin between two groups.

3.2. Time course of urinary renal biomarkers after dosing of cisplatin

In patients with more than 20% decrease in eGFR during 6 days after dosing of cisplatin, traditional renal damage markers such as Scr was significantly higher on day 6, but not on day 3. On the other hand, urinary vanin-1 significantly elevated early on day 3 in patients with the decreased eGFR. Of note, significant difference was not detected in urinary vanin-1 at baseline between the two

Table 1
Treatment details of GC regimen.

Drugs, Fluid	Infusion time	Day 1	Day 2	Day 3	Day 8
Lactate Ringer solution (Solacet F®), 500 mL	5	9:00	5:00	5:00	9:00
Metoclopramide (Primperan®), 10 mg		20:00	20:00		
Maintenance fluid (Soldem 3A®), 500 mL	5	13:00	10:00	10:00	
		23:00	23:00		
Lactate Ringer solution (Perol®), 500 mL	5	17:00	15:00	15:00	
Ramosetron (Nasea®), 0.3 mg Normal saline, 100 mL		9:30	9:30		9:30
Furosemide (Lasix®), 20 mg	i.v.	9:30	9:30	9:30	
		13:00			
		19:00	19:00		
Methylprednisolone sodium succinate (Pridol®), 125 mg Normal saline, 100 mL	0.5	18:00	18:00		
Gemcitabine hydrochloride (Gemzar®), 1000 mg/m^2 Normal saline, 100 mL	0.5	10:00			10:00
Cisplatin (Randa®), 70 mg/m^2	3	10:30			
10% NaCl 20 mL					

GC, gemcitabine and cisplatin.