RESEARCH ARTICLE

Evaluation of Renal Function Using the Level of Neutrophil Gelatinase-Associated Lipocalin is Not Predictive of Nephrotoxicity Associated with Cisplatin-Based Chemotherapy

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Abstract

Background: For early detection of renal damage during the usage of cisplatin based chemotherapy, changes in renal function should be monitored carefully. In recent years, neutrophil gelatinase-associated lipocalin, a small polypeptide molecule, has shown promise as a marker of acute renal failure. The aim of this present study was to assess possible risk prediction of cisplatin-induced nephrotoxicity using serum NGAL. Materials and Methods: A total of 34 consecutive patients with documented serum creatinine at least 24 hours before every cycle of cisplatin-based chemotherapy were included in the study. Demographic and medical data including age, performance status, tumor characteristics and comorbid diseases were collected from medical charts. Renal function was evaluated at least 48 hours before the treatment and at the end of the treatment based on the Modification of Diet in Renal Disease (MDRD) formula. Before and after cisplatin infusion serum NGAL levels were measured for the first and 3rd cycles of chemotherapy. Results: The median age of the study population was 54 (32-70) years. Fifteen patients (41.1%) were treated on an adjuvant basis, whereas 19 patients (58.9%) were treated for metastatic disease. There was no correlation of serum NGAL levels with serum creatinine (r=0.20, p=0.26) and MDRD (r=-0.12, p=0.50) and creatinine clearance-Cockcroft-Gault (r=-0.22, p=0.22) after cisplatin infusion at the end of the 3rd cycle of chemotherapy. Conclusions: In our study, serum NGAL levels were not correlated with the cisplatin induced nephrotoxicity. Further prospective studies are needed to conclude that serum NGAL level is not a good surrogate marker to predict early cisplatin induced nephrotoxicity.

Keywords: Chemotherapy - cisplatin - neutrophil gelatinase-associated lipocalin

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Introduction

Although cisplatin accumulates in all nephron segments, most of the damage occurs in the S3 segment, which contains proximal tubule cells (Townsend et al., 2003). Since this effect is dose-dependent and cumulative, its dose is limited in treatment (Hanigan et al., 2003). Although some methods have been tried in preventing cisplatin-induced nephrotoxicity, none of them has been widely accepted yet (Asna et al., 2005). Therefore, during the use of cisplatin, the changes in the renal function should be closely monitored for early diagnosis of the renal damage (Perazella et al., 2010).

The methods based on exogenous substance clearance in monitoring the renal function are not favored in routine use because of the high cost and the difficulty of application in every health centers (Mohanram et al., 2005). Instead, the blood creatinine and creatinine clearance are preferred to evaluate the renal function (Perrone et al., 1992). However, these methods have some limitations such as the need of secretion of creatinine from the glomerules and patient incompatibility in collecting 24-hour urine (Shemesh et al., 1985). Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) formulations, which take into account additional variables such as the age, gender, race and muscle mass are developed in order to facilitate and increase the sensitivity of serum creatinine-based glomerular filtration rate (GFR) measurement (Levey et al., 1999).

Neutrophil gelatinase-associated lipocalin (NGAL), a polypeptide bonded with matrix metalloproteinase (MMP) in neutrophils (Kjeldsen et al., 1994), is a promising indicator in acute renal failure (Mishra et al., 2003). NGAL is secreted from the thick-ascending limb of Henle's loop and collecting tubules into the urine. The secretion of this 25-kDa protein is induced from the renal tubule cells during the regeneration phase following renal damage (Kuwabara et al., 2009). There are some studies regarding

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NGAL use as an early indicator in acute renal failure associated with cardiac surgery, the use of contrast agent and renal transplantation (Parikh et al., 2006; Wagener et al., 2006; Ling et al., 2008). However, there are limited studies in its use in chemotherapeutic agent-induced acute renal failure (Mishra et al., 2004).

The aim of our study was to assess the correlation between serum NGAL levels and serum creatinine and GFR calculated by Cockcroft-Gault and MDRD formulary in patients who underwent cisplatin-induced chemotherapy and to evaluate its potential use in the early diagnosis of renal function changes.

Materials and Methods

Patients and treatments

A total of 34 patients with various malignancies, who underwent cisplatin-based chemotherapy for adjuvant and palliative treatment, were included in this study. None of the patients received any chemotherapy previously. Based on the malignancy types, five different chemotherapeutic regimens were administered. The dose and administration route of modified DCF (mDCF), CF, CFF cisplatin-taxoter and gemcitabine-cisplatin protocols are shown in Table 1. In order to determine creatinine levels, blood samples were obtained before the treatment, at the end of cisplatin infusion, and when the third cycle was completed. NGAL levels were obtained before the chemotherapy and at the end of cisplatin infusion. The personal information such as weight, age and gender were gathered at the beginning of the first cycle and following the third cycle in order to be used in Cockcroft-Gault and MDRD formulary.

Laboratory methods and the formulary

Serum creatinine levels were determined with Beckman DXC 800 autoanalyzer using Jaffe method. The reference range was 0.6-1.3 mg/dL. The serum NGAL level was measured with ELISA method using Biovendor Human Lipocalin-2 /NGAL® kit. Since the samples were diluted, the sample concentration results that were calculated by standard curve were multiplied by dilution factor (Dilution factor: 30). The creatinine clearance was calculated by Cockcroft-Gault Formulary as shown below.

Creatinine clearance (mL/min)=[(140-Age)x Actual weight (kg)xR]/[72xserum creatinine(mg/dL)]; R coefficient is 1 for males and 0.85 for females. The following equation was used to calculate GFR using MDRD. GFR [mL/min/1.73m^2]=175×[Serum Creatinine (mg/dL)]–1.154×(Age)–0.203×R; R coefficient is 1 for males and 0.742 for females.

Statistical analysis

The demographic data and findings were presented as standard deviations (SD) and 95% confidence intervals (CI), and means and medians. The variables were compared using Mann-Whitney test. The statistical differences among the measurements were analyzed by Student's T-test. Correlations were evaluated with parametric Pearson and nonparametric Spearman correlation tests. A P-value less than 0.05 was considered statistically significant. The data were analyzed using Statistical Packages for Social Sciences (SPSS version 13.0).

Results

A total of 34 patients, 20 (58.8%) males and 14 (41.2%) females were included in the study. The median age was 54 years (the range was between 14 and 70). Of the patients, 20 (58.8%) had gastric cancer and this was the most frequent malignancy in this patient group. The other malignancies were head and neck cancers (n=8, 23.5%), lung cancer (n=3, 8.8%), esophagus cancer (n=2, 5.9%) and cholangiocellular cancer (n=1, 2.9%). Fifteen (41.1%) patients received adjuvant therapy and 19 patients had metastasis at the time of diagnosis. Based on their diagnosis and the grades, 21 (61.8%) received DCF, 7 (20.6%) received CFF, 3 (8.8%) received CF, 2 (5.9%) received gemcitabine-cisplatin and 1 received cisplatin-taxotere treatment protocol (Table 2).

The mean serum creatinine level was 0.76±0.20 mg/dL and mean serum NGAL level was 125.5±54.5 ng/ml prior to the chemotherapy. The creatinine clearance calculated by Cockcroft-Gault formulary was 102.5±37.6 ml/min and GFR calculated by MDRD was 109.9±37.9 ml/min/1.73 m^2. The mean NGAL level was 139.4±51.0 ng/ml following the first cycle of cisplatin infusion. The mean creatinine level was 0.74±0.16 mg/dL following the third cycle. The creatinine clearance was 100.3±31.1 ml/min by Cockcroft-Gault method and GFR calculated by MDRD was 110.1±26.8ml/min/1.73 m^2 (Table 3).

There were no statistically significant linear correlations between serum NGAL and serum creatinine levels prior to the chemotherapy and also between MDRD and creatinine clearance by Cockcroft-Gault method (r=0.16 and p=0.36, r=-0.05 and p=0.79, r=-0.25 p=0.16 respectively) (Figure 1A-1C). No correlations were determined between NGAL levels after the cisplatin infusion and the following

Table 1. Chemotherapeutic Regimens, Doses and Protocols

Regimens	Doses and Protocols
Modified DCF (mDCF)	60 mg/m^2 docetaxel on day 1 and 60 mg/m^2 cisplatin on day 1 and 600 mg/m^2/day 5 fluorouracil (5-FU) continuous infusion with pump for 5 days, every 3 weeks
CF	75 mg/m^2 cisplatin on day 1 and 750 mg/m^2 5-FU on day 1-4, every 4 weeks
CFF	50 mg/m^2 cisplatin on day 1 and 200 mg/m^2 folinic acid on day 1 and 400 mg/m^2 5-FU intravenous (IV) bolus on day 1 and 1600 mg/m^2 5-FU continuous infusion with pump for 2 days, every 2 weeks
Cisplatin-taxotere	80 mg/m^2 cisplatin on day 1 and 75 mg/m^2 taxotere on day 1, every 3 weeks
Gemcitabin-cisplatin	75 mg/m^2 cisplatin on day 1 and 1200 mg/m^2 gemcitabin on day 1,8, every 3 weeks

Table 2. Patient Characteristics (n=34)

		n (%)
Age (years)	Median (range)	54 (32-70)
Diagnosis	Gastric cancer	20 (58.8)
	Head and neck cancers	8 (23.5)
	Lung cancer	3 (8.8)
	Esophagus cancer	2 (5.9)
	Cholangiocellular cancer	1 (2.9)
Metastasis	No	15 (41.1)
	Yes	19 (55.9)
Treatment	DCF	21 (61.8)
	CFF	7 (20.6)
	CF	3 (8.8)
	Gemcitabine-cisplatin	2 (5.9)
	Cisplatin-taxotere	1 (2.9)

Table 3. Biochemical Findings (n=34)

	Measured Values	
	Mean±SD	95% CI
Serum creatinine (mg/dL)		
Before chemotherapy	0.76±0.20	0.69-0.83
After 3rd cycle	0.74±0.16	0.68-0.80
Serum NGAL (ng/ml)		
Before chemotherapy	125.5±54.5	12.3-217.8
After 1st cisplatin infusion	139.4±51.0	54.9-264.6
Creatinine clearance - Cockcroft-Gault (ml/min)		
Before chemotherapy	102.5±37.6	80.4-115.7
After 3rd cycle	100.3±31.1	89.4-111.1
MDRD (ml/min/1.73 m^2)		
Before chemotherapy	109.9±37.9	96.7-123.1
After 3rd cycle	110.1±26.8	100.7-119.5

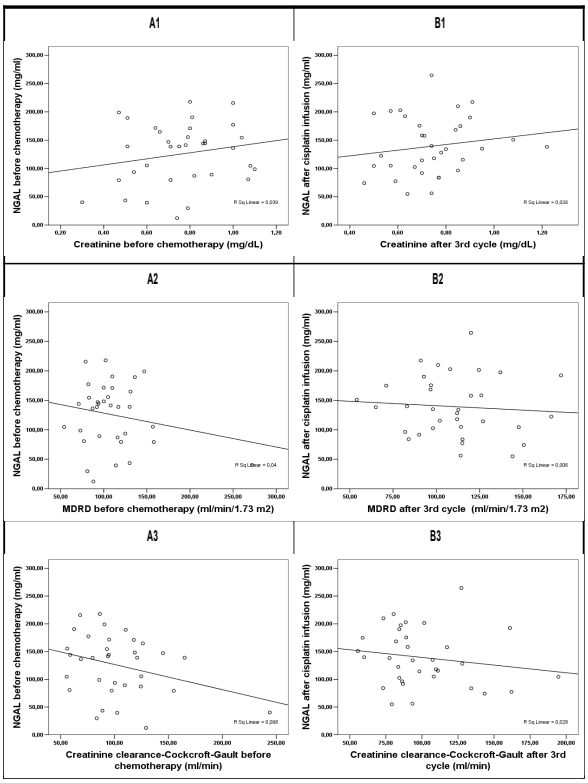

Figure 1. Associations Between Pairs of Variables. Serum NGAL and Creatinine Levels Prior the Chemotherapy (1A), and GFR Calculated by MDRD (1B) and by Creatinine Clearance-Cockcroft-Gault (1C) Formula in Scatter Plots. Association among the Serum NGAL Levels Following Cisplatin Infusion and the Creatinine Levels after the Third Cycle (2A), and GFR Calculated by MDRD (2B) and by Creatinine Clearance-Cockcroft-Gault (2C) Formula in Scatter Plots

parameters: serum creatinine levels following the third cycle (r=0.20, p=0.26), MDRD (r=-0.12, p=0.50), and creatinine clearance by Cockcroft-Gault method (r=-0.22, p=0.22) (Figure 2A-2C). The levels of NGAL prior to the chemotherapy or following the cisplatin infusion did not reflect the impairment of renal function (the increase of serum creatinine, the decrease of GFR calculated by MDRD, and by creatinine clearance using Cockcroft-Gault method) following the third cycle.

Discussion

This study demonstrated that the serum NGAL level is not an appropriate parameter to predict the impairment of renal function during chemotherapy.

The preclinical studies showed that urinary NGAL levels were increased based on the dose and duration during three-hour cisplatin infusion in the rat model of cisplatin-induced nephrotoxicity (Mishra et al., 2004). A previous clinical study evaluated the role of NGAL in the follow-up of cisplatin-induced renal damage. In the study of Gaspari et al. (2010) the urinary NGAL levels of 12 patients, whose serum creatinine levels were increased by 25% over of the basal level during cisplatin infusion, were higher than the group without renal failure on the 1st, 2nd, 3rd and 15th days following the cisplatin infusion (Gaspari et al., 2010). Prolonged renal failure was present in half of these patients.

Due to the concern of renal failure following the use of chemotherapeutic agents, either the dose of medicine is decreased, or doses are skipped and cycle intervals are prolonged, and as a result of these, the efficacy is diminished. Therefore, early prediction of predisposition to renal function impairment and taking precautions early are crucial. The rationale of our study's design was based on that. We think that determining the cumulative toxicity by a parameter measured following the first administration is crucial. However, our findings did not meet our expectations. There were no linear correlations among serum NGAL levels following the cisplatin infusion, serum creatinine levels following the third cycle and GFR calculated by MDRD and by creatinine clearance-Cockcroft-Gault formularies.

Further studies with larger number of cancer patients can help us to understand whether serum NGAL level is a useful method or not in the early detection of cisplatin-induced renal damage.

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