Brief Report

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The potential effects of non-renal factors, glucocorticoid treatment and hematological malignancies, on serum cystatin C level

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Abstract

Cystatin C as a novel marker of kidney function may have some drawbacks in clinical practice. The aim of the present study was to assess the impact of glucocorticoid therapy and hematological malignancies on serum cystatin C level in patients receiving amphotericin B. Forty five adult patients with no history of acute or chronic kidney injury planned to receive conventional amphotericin B for an anticipated duration of at least 1 week for any indication were included. At the time of amphotericin B treatment, serum cystatin C as well as creatinine levels, were measured at days 0, 7, and 14. There was no statistically significant association between hematological malignancies and elevated serum Cys C at days 0 (P=0.0705), 7 (P=0.679), and 14 (P=1). The mean±SD serum Cys C levels at the three time points were comparable between patients receiving glucocorticoids and those not having been given glucocorticoids. Our findings suggested that glucocorticoid treatment and hematological malignancies appear to have no significant effect on the serum cystatin C level in patients recieving amphotericin B treatment.

Keywords: Glucocorticoid, Hematological malignancies, Serum cystatin C.

1. Introduction

Serum creatinine as a classic marker of renal function suffers from several limitations. Many non-renal factors such as age, gender, race, protein intake, muscle mass, infections, and inflammatory status may potentially affect serum creatinine (1). To circumvent drawbacks of serum creatinine in the setting of acute kidney injury (AKI), several novel biomarkers of renal functions such as cystatin C (Cys C), a non-glycosylated protein with cysteine proteinase inhibitor activity, have been extensively investigated. These studies have been associated with promising findings in certain clinical settings such as renal transplant recipients and liver disease (1, 2). Despite its superiority compared to serum creatinine, applying serum Cys C as a marker of renal function in clinical practice is not without drawbacks. Some of these limitations included the probable effects of non-renal factors on this marker (3). The aim of the present study was to evaluate the plausible influence of glucocorticoid treatment and hematological malignancies on serum Cys C level in patients receiving amphotericin B.

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2. Methods

This study is a part of a multicentre randomized, double-blinded, placebo-controlled, clinical trial (ID: IRCT201107233449N8) having been described in detail previously (4). In brief, it was performed within 15 months at 3 university health-care settings affiliated to Tehran University of Medical Sciences, Tehran, Iran. The cohort included adult in-patients planned to receive conventional amphotericin B for an anticipated dura-

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tion of at least 1 week for any indication. They had no documented history of AKI or chronic kidney disease. Recruited patients had negative history of receiving amphotericin B by any administration route within the recent 14 days.

Serum Cys C as well as creatinine levels were measured at 3 time points during amphotericin B treatment (days 0, 7, and 14). Measurement of serum creatinine was performed by an Auto-analyzer (Biotechnica BT-3000, Italy) based on the modified Jaffe colorimetric reaction. Serum Cys C level was determined by the turbidimetric method (Gentian, Moss, Norway). Based on the package insert of serum creatinine reagent (Pars Azmun, Karaj, Iran), 0.7-1.4 mg/dL and 0.6-1.3 mg/dL were considered as reference range of serum creatinine for male and female patients, respectively. According to Cys C turbidimetric assay kit, 0.51-1.05 mg/L was the reference range for serum Cys C in both sexes. White blood cell (WBC) count at days 0, 7, and 14 were also determined. Glomerular filtration rate (GFR) was calculated by the Cockcroft-Gault formula.

2.1. Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. Chi square or Fisher exact test was exploited to evaluate possible associations of categorical variables. Plausible association between the median WBC count and elevated serum Cys C was examined by the Mann-Whitney test. Spearman test was exploited to assess the correlation between WBC count and serum Cys C. Multivariate logistic regression analysis was used to calculate odds ratio (OR) and their 95% confidence interval (CI) of independent variables including WBC count, hematological malignancies, and glucocorticoid treatment. *P* values<0.05 were considered as statistical significance. All the above statistical analyses were carried out by the SPSS (Statistical Package for the Social Sciences) version 20 software.

3. Results

Among 54 patients recruited into the study, 44 (81.5%) had hematological malignancies. The diagnosis included acute myeloid leukemia (AML, n=25), acute lymphoid leukemia (ALL, n=11), non-Hodgkin lymphoma (n=4), chronic leukemia (n=2), Hodgkin lymphoma (n=1), and myelodysplastic syndrome (n=1). According to Fisher's Exact test, there was no statistically significant association between hematological malignancies and elevated serum Cys C at days 0 (P=0.0705), 7 (P=0.679), and 14 (P=1).

The number of patients with elevated serum Cys C was higher than those with elevated serum creatinine at days 0, 7, and 14 of amphotericin B treatment (70.37%, 53.66%, and 78.57% vs. 27.78%, 34.15%, and 71.43%, respectively). However, these differences did not reach the level of statistical significance (P=0.705, P=0.731, and P=1, respectively).

Among the cohort, 22 (40.74%) individuals received intravenous glucocorticoids including dexamethasone and hydrocortisone. The mean ± SD amount of administered glucocorticoid per day equivalent to prednisolone dose was 80.49±48.63 mg (range, 12.5-160 mg). The mean±SD serum Cys C levels in days 0, 7, and 14 did not differ significantly between patients receiving glucocorticoids and those not having been given glucocorticoids (Table 1). The GFR values at relevant time points were also comparable between the two groups (103.12±37.06 vs. 85.93±44.35 ml/min; P=0.141 [day 0], 90.05±39.64 vs. 93.8±50.63 ml/min; P=0.774 [day 7], and 49.2±10.52 vs.

Table 1. The possible association between serum cystatin C level and glucocorticoid treatment at different time points of the study.

Time point	Serum cystatin C, Mean±SD (mg/L)		*P* value
	With glucocorticoid	Without glucocorticoid	
Day 0	1.31±0.33	1.14±0.41	0.099
Day 7	1.42±0.64	1.25±0.67	0.407
Day 14	1.18±0.84	1.32±0.44	0.68

57.11±24.72 ml/min; P=0.514 [day 14]).

The results of Mann-Whitney test indicated that the median (interquartile range) WBC count at days 0, 7, and 14 was comparable between patients with normal and elevated serum Cys C levels (P=0.607, P=0.207, and P=0.61, respectively). The correlation between WBC count and serum Cys C level at days 0 (r=0.15), 7 (r=0.2), and 14 (r=0.07) was also not statistically significant (P=0.27, P=0.21, and P=0.83, respectively).

In line with univariate analysis, the results of multivariate logistic regression model demonstrated that there was no statistically significant association between elevated serum Cys C and WBC

Table 2. The possible association between elevated serum Cys C and white blood cell count, hematological malignancies, and glucocorticoid therapy at different time points of the study.

Variable	Normal serum cystatin C	Elevated serum cystatin C	OR (95% CI)	P value
Day 0				
White blood cell count (/mm^3)				
Median (Interquartile Range)	5000 (11800)	6000 (6525)	0.961 (0.895-1.031)	0.269
Glucocorticoid therapy (%)				
Yes	5 (31.25)	17 (44.74)	2.272 (0.59-8.755)	0.233
No	11 (68.75)	21 (55.26)		
Hematological malignancies (%)				
Yes	14 (87.5)	30 (78.95)	2.17 (0.388-9.151)	0.378
No	2 (12.5)	8 (21.05)		
Day 7				
White blood cell count (/mm^3)				
Median (Interquartile Range)	8000 (2000)	1400 (11500)	0.989 (0.945-1.034)	0.615
Glucocorticoid therapy (%)				
Yes	6 (33.33)	10 (43.48)	1.612 (0.439-5.922)	0.472
No	12 (66.67)	13 (56.52)		
Hematological malignancies (%)				
Yes	14 (77.78)	20 (86.96)	0.507 (0.096-2.664)	0.422
No	4 (22.22)	3 (13.04)		
Day 14				
White blood cell count (/mm^3)				
Median (Interquartile Range)	82500 (12200)	4200 (9580)	1.003 (0.883-1.14)	0.961
Glucocorticoid therapy (%)				
Yes	3 (60)	4 (40)	3.946 (0.199-8.109)	0.367
No	2 (40)	6 (60)		
Hematological malignancies (%)				
Yes	4 (80)	8 (80)	2.014 (0.09-5.227)	0.659
No	1 (20)	2 (20)		

Odds ratio (OR), Confidence interval (CI)

count, glucocorticoid therapy, and hematological malignancies in days 0, 7 and 14 of amphotericin B treatment (Table 2).

4. Discussion

Regarding the probable effects of glucocorticoid treatment, a number studies in renal transplant recipients (5), individuals with asthma (6), Graves' ophthalmopathy (7), and subarachnoid hemorrhage (8), demonstrated that administration of glucocorticoids such as oral prednisolone and parentral methylprednisolone at dose ranges between 100-500 mg daily was associated with an increase in serum Cys C level. However, this association was not observed in other clinical settings such as lupus nephritis (20-60 mg/m2/day prednisone) (9) and nephrotic syndrome (0.5 mg/kg/day prednisone or methylprednisolone) (10). As suggested by Silva et al, this discrepancy may be due to lack of an accepted reference standard for renal function in these studies (9). In the current survey, there was no significant association between the use of glucocorticoids and serum Cys C levels at different studied time points of amphotericin B treatment course even after considering relevant GFR values. The daily amount of glucocorticoids equivalent to prednisolone dose administered to our cohort (12.5-160 mg) was relatively within the range used in the aforementioned studies (100-500 mg).

It has been demonstrated that serum Cys C levels in patients with solid tumors including ovarian cancer (11), colorectal cancer, and melanoma (12) is significantly higher than non-malignant individuals with comparable renal function. However, Stabuc *et al*. reported that metastasis had no significant effect on serum Cys C levels in adult patients with solid tumors like gastric cancer, ovarian cancer, and malignant melanoma (13). Data regarding this issue in patients with hematologic malignancies are quietly scarce. A preliminary study performed by Demirtas et al. in leukemic patients underwent bone marrow transplantation (BMT) and received a number of nephrotoxic agents such as amphotericin B implicated that measured serum Cys C levels after BMT were significantly higher than control individuals. Furthermore, serum Cys C did not correlate significantly with neither serum creatinine nor creatinine clearance. The authors suggested that elevated serum Cys C levels in leukemic patients may be due to its increased synthesis by the malignant cells rather than decrease in its renal clearance. Therefore, serum Cys C appears not to be an appropriate marker of renal function in leukemic patients receiving nephrotoxic agents such as amphotericin B (14). In contrast, at least one report from the setting of hematologic malignancies suggested serum Cys C as a suitable marker of glomerular function in children with leukemia or solid tumors (15). Bardi et al. demonstrated that serum Cys C levels before corticosteroid treatment in children with ALL was significantly higher than that in individuals with acute idiopathic thrombocytopenic purpura (1.23±1.12 and 0.96±0.27 mg/L, respectively; P=0.02). Interestingly, pre corticosteroid treatment WBC values of patients with ITP was significantly lower than that of patients with ALL (P=0.03) and there was a significant correlation (r2=0.06, P=0.04) between pretreatment serum Cys C and WBC values in patients with ALL. The authors justified these findings by tumor lysis syndrome and infiltration of the kidneys with the leukemic blast cells in children with ALL (but not ITP) which both are proportional to WBC counts (16). In the current survey with more than 90% of our cohort being involved with hematologic malignancies, we identified a clinically, but not statistically, significant difference in the number of patients with elevated serum Cys C than those with elevated serum creatinine at day 0 (38 versus 15 subjects, respectively). Probable increased synthesis by malignant cells may be taken into account for this finding. However, there is no statistically significant association between WBC count and elevated serum Cys C in the 3 studied time points. In addition, no significant correlation between WBC count and serum Cys C levels was identified in our cohort. Lack of a certain and reliable reference range for serum Cys C in Iranian population and non-reliability of the range cited in the package insert of Cys C turbidimetric assay kit provided by the Gentian company (0.51-1.05 mg/L), may question the number of patients having had elevated serum Cys C levels in our cohort. Finally, limited number of serum Cys C level measurements at only three time points within

amphotericin B treatment (days 0, 7, and 14) may not reflect the real status of its changing trend and subsequently, renal function in our patients. Much higher intraindividual variability with serum Cys C compared to serum creatinine, observed in at least one study [e.g. 75% versus 7%, respectively (17)] can highlight the importance of this issue.

In conclusion, our preliminary study suggested that glucocorticoid treatment and hematological malignancies appear to have no statistically significant effect on the serum Cys C levels in patients receiving amphotericin B. However, the definite role of serum Cys C as a favorable marker of renal function in patients with hematological malignancies remains equivocal and uncertain. More studies are warranted in this area.

Conflict of Interest

None declared.

5. References

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