Serum CEA level is associated comorbidity of hemodialysis patients

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Abstract: Hemodialysis affects biomarkers concentration in blood. The aim of this study is to evaluate the effects of hemodialysis on commonly used tumor markers. A total of 28 unselected patients (22 men and 6 women) with end-stage renal disease (ESRD), treated with maintenance hemodialysis, were enrolled in this study. GOT and tumor markers such as CA-153, CA-125, and CEA are measured. The mean age was 57.6 ± 12.6 years with 51.0 ± 34.0 months hemodialysis duration. Our results indicated that tumor marker CEA level is correlated to Charlson's score of hemodialysis patients whereas level of CA153 and CA125 is not correlated to age, duration of dialysis and Charlson's score. GOT level is correlated to age, and Charlson's score. In conclusion, concentration of CEA is correlated with Charlson's score which strongly correlated with hemodialysis outcome. GOT value is correlated with age and Charlson's score which implies liver function drop in long term hemodialysis patients.

Keywords: biomarkers, End-Stage Renal Disease, hemodialysis, serum.

1. Introduction

Hemodialysis is widely used for kidney failure induced by variety of underlying causes including diabetes, hypertension, and glomerulonephritis. The dialysis membrane in artificial kidney tube filtrates out small molecules especially for small molecular weight proteins (i.e., <40 kDa). On the other hand, larger molecular weight proteins, e.g., tumor markers, are remaining in the blood, and had been evaluated in hemodialysis patients [1, 2]. The detection of tumor markers is important for cancer surveillance and follow–up, however, diagnostic validity of those markers are uncertain in hemodialysis patients. There are reports indicate that serum level of tumor markers change after long term hemodialysis due to absorption of dialysis membrane, liver, kidney, or other organ's metabolism but the variation trends are uncertain for each biomarker [3]. Study of serum levels of five tumor markers, including the soluble cytokeratin 19 fragment (CYFRA), pro-gastrin-releasing peptide (ProGRP), serum levels of CYFRA and ProGRP together with conventional markers including

carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), neuron specific enolase (NSE), for lung cancer in patients with chronic renal failure indicate that mean concentration of CYFRA, CEA, SCC, and NSE except ProGRP were significantly increased with the severity of renal failure, and suggested a high false positive rates for tumor markers of lung cancer in patients with renal failure [2]. Recent studies of the diagnostic validity of prostate-specific antigen (PSA) among man receiving hemodialysis shows dialysis induced elevations in all forms of PSA immediately after hemodialysis [4]. However, Horinaga *et. al.* [5] shows that cancer-free hemodialysis man demonstrated significantly lower PSA compared to controls. Here we examine the serum level of commonly used molecular biomarkers, such as CA-153, CA125, CEA, and GOT of hemodialysis patients.

2. Material and Methods

Patient characteristics. Experiments performed in this study complied with the current laws and

regulations in Taiwan, Republic of China. All procedures are followed by the ethnical guideline and approved by Kaohsiung Armed Forces Hospital committee, Taiwan. A total of 28 persons between the ages of 37 and 76 years with end-stage renal disease, receiving dialysis treatment three times per week, were enrolled in a prospective study in March 2008. Dialysis was carried out using a Nikkiso DBB-22B dialysis machine with 4 hours session. Dialyzer with APS 18MD (Asahi Kasei, Osaka, Japan, polysulfone membrane, surface area 1.8 m^2, *in vitro* clearances for urea, 198 ml/min for QB-200 ml/min). Blood flow rate was setting at 200 ml/min. Patients with vascular success insufficiency which can't reach required blood flow rate was excluded. Ultrafiltration rate (512±85 ml/h) was adjusted according to the patients' needs. The flow and temperature of the dialysate was 500 ml/min and 37°C, respectively. Vascular access was either via an arterio-venous fistula (sixteen treatments), graft (nine treatments), or a Perm catheter (three treatment). Serum CA-153, CA125, CEA, GOT levels were measured before and immediately after HD using low-flux membrane.

Blood/serum collection. Serum samples were collected from hemodialysis patients during and after the course of HD treatment. 5 ml blood was collected in EDTA tube. The serum were then stored in 4°C and processed within 12 hours. The serum samples were centrifuged at 2000 rpm for 10 min prior to splitting into aliquots and stored at -20°C.

The serum levels of CA-153, CA125, CEA and GOT were measured with Abbott Axsym analyzer (Abbott Laboratories, Abbott Park, III). The reference ranges of the markers were: CA-153, 0-31.3 U/ml; CA-125, 0-35 U/ml; CEA, 0-3 ng/ml for non-smoker, and 0-5 ng/ml for smoker; GOT, 0-32 U/L.

The data reported are means ± standard deviations (SD). Pearson correlation coefficient (r) was used for analyses of linear associations. Because the concentrations of serum tumor markers were not normally distributed, significance of differences was assessed by Wilcoxon Matched-Pairs Signed-Ranks Test. The level of statistical significance was always set at P<0.05. Statistical analysis was performed using the statistical package Sigma Stat 3.1 (Systat Software, Inc., San Jose, CA, USA).

3. Results

Baseline demographic and clinical data. We analyzed 28 patients, of which 22 were men and 6 were women. The demographic and clinical data are summarized in Table 1. All patients are diagnosed as end-stage renal failure. The mean age was 57.8 ± 12.6 years. Mean dialysis vintage was 51.0 ± 34.0 months.

Measurement of tumor marker concentration of patients before and after hemodialysis. The mean

value of CA-153 was 16.5±16.3 before hemodialysis and 18.6±16.3 after hemodialysis. The CA-125 level was 35.2±38.9 before dialysis and 34.3±41.2 after hemodialysis. Thee GOT level was 22.1±10.6 before hemodialysis and 27.5±11.7 after hemodialysis. The level of CEA was 6.2±7.7 before hemodialysis, and 6.0±8.0 after hemodialysis *Correlates of serum markers.* Correlations between serum markers levels and age, duration of dialysis and Charlson's score are measured. CEA level was correlated with Charlson's score (r=0.42, p=0.03) (Fig. 1). GOT level was correlated with age (r=0.42, p=0.02) (Fig. 2A) and Charlson's score (r=0.48, p=0.01) (Fig. 2B). Other variables, including CA-153.
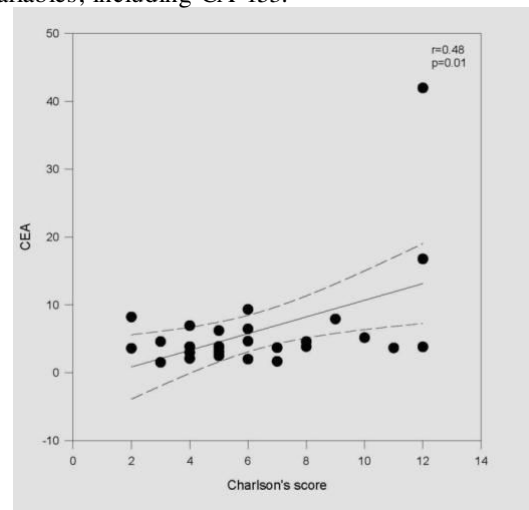

Figure 1. Scatter plots, regression line, and 95% confidence intervals reflecting correlations between serum levels of CEA and Charlson's score of 28 HD patients.
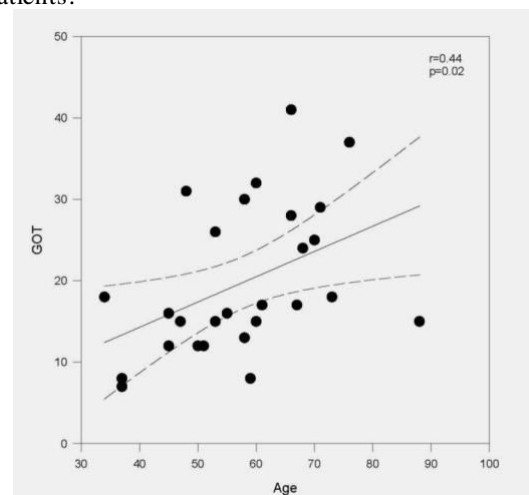

Figure 2. Scatter plots, regression line, and 95% confidence intervals reflecting correlations between serum levels of GOT and Charlson's score of 28 HD patients.

CA125 is not correlated with age, duration of HD, and Charlson's score (Table 2). *Direct effect of hemodialysis on concentration of serum markers.* Wilcoson signed rank tested is chosen to compare groups of serum markers before and after hemodialysis. The levels of CA-153, CA125, CEA, and GOT before hemodialysis are not significantly different to that after hemodialysis (Table 3).

4. Discussion

CA-153, CA-125, CEA are commonly used as tumor markers. CA-125 is a glycoprotein with high molecular weight (> 200 kDa), and is a cancer antigen for monitor mesothelium especially for ovarian cancer. Recently, CA-125 is used to monitor mesothelial cell viability in PD patients [6, 7]. CEA is carcinoembryonic antigen with a molecular weight about 180-200 kDa, commonly used for monitoring gastric cancer [8]. Report indicated that CEA was weakly correlate with carotid atherosclerosis [9], PD patients [6, 7]. CEA is carcinoembryonic antigen with a molecular weight about 180-200 kDa, commonly used for monitoring gastric cancer [8]. Report indicated that CEA was weakly correlate with carotid atherosclerosis [9], and with prognostic value of colorectal cancer in PD patients [10]. The mean value of CEA of 28 patients is higher than normal value, which is consistent with previous reports that patients with ESRD are usually with higher risk of cancer, and with higher levels of tumor markers [11]. In our cases, patient no.2, 5, 9, 13 and 27 were expired within 1 year after diagnosis. Patient no. 2 is finally diagnosed as hepatoma, patient no. 5 is cirrhosis of liver and died in septicemia, patient no. 9 is died in leukemia, and patient no 13 is died in lung cancer. It shows that high levels of CEA correlated with Charlson's score which implies poor outcome, however it remain further confirmation. CA-153 is correlated to risk of liver disease. Though 8% patients were diagnosed liver diseases, but their GOT value fall in normal range, and CA-153 values of them were also normal.

There are many reports indicated that long term hemodialysis may affect levels of biomarkers. We showed that no overt alternation of serum biomarkers after hemodialysis. It is interesting that recent report indicated acute effects of hemodialysis treatment on up- or down-regulation of apoptotic genes in blood leucocytes [12]. Tumor markers were produced by neoplastic cells, and can also be secreted by normal tissue. Many chronic diseases such as inflammation, chronic bronchitis, cirrhosis of liver and renal diseases affect the metabolism and elimination of tumor markers. Our data show that the effect of hemodialysis on biomarkers of patients is not significant. And all 4 serum markers are not correlated with duration of hemodialysis. It seems that

hemodialysis does not directly affect levels of these serum markers. However, CEA and GOT are shown to be candidates markers for monitoring hemodialysis outcome as they are positively correlated with Charlson's score.
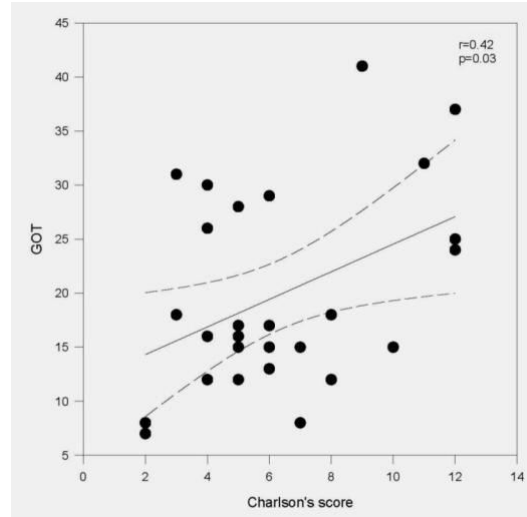

Figure 3. Scatter plots, regression line, and 95% confidence intervals reflecting correlations between serum levels of GOT and age of 28 HD patients.

Table I. Baseline demographic and clinical data

N=28	
Sex (M: F)	22::6
Age (years)	57.8 ± 12.6
Duration of dialysis (months)	51.0 ± 34.0
Body height (cm)	164.0 ± 7.5
Body weight (kg)	66.2 ± 13.2
Body mass index (kg/m2)	23.7 ± 4.5
Renal diagnosis, no. cases (%)	
Glomerulonephritis	43
Diabetic nephropathy	29
Polycystic kidney	14
Hypertensive nephrosclerosis	4
Gouty nephropathy	
Major comorbidity, no. cases (%)	39
Diabetes mellitus	36
Ischaemic heart disease	4
Cerebrovascular disease	14
Peripheral vascular disease	4
Moderate or severe liver disease	11
Any tumor, leukemia, lymphoma	7
Modified Charlson's comorbidity score*	6.3± 3.3
Dialysis adequacy	
Total Kt/V	1.3 ± 0.4
Residual GFR (mL/min per 1.73 m2)	6.8 ± 3.5
NPCR (g/kg per day)	1.3 ± 0.4
Cr (mg/dl)	9.1 ± 2.8

GFR, glomerular filtration rate; NPCR, normalized protein catabolic rate, *Modified Charlson's comorbidity score is calculated according to Beddhu S, 2000.

Table II. Correlation of serum markers and age, duration of HD, and Charlson's score.

Age of patients			Duration of HD	Charlson's score
CA153	0.0688		-0.162	0.313
	p value	0.728	0.409	0.105
CA125	0.202		-0.139	0.202
	p value	0.302	0.48	0.302
CEA	0.264		-0.132	0.475
	p value	0.175	0.50	0.0106
GOT	0.436		-0.0682	0.422
	p value	0.020	0.73	0.0254

Table III. Comparison of serum tumor markers before and after hemodialysis

Bio Markers	Hemodialysis	Mean ±SD (n-13)	P-value
CA-153	Before	16.5±16.3 (U/ml)	0.75
	After	18.6±16.3 (U/ml)	
CA125	Before	43.0±48.6 (U/ml)	0.99
	After	47.3±51.7 (U/ml)	
CEA	Before	5.9±4.0 (ng/ml)	0.42
	After	6.6±4.6 (ng/ml)	
GOT	Before	24.0±11.0 (U/ml)	0.76
	After	27.5±11.7 (U/ml)	

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