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Impact of vascular endothelial growth factor on prognosis of patients with hepatocellular carcinoma treated with angiotensin-converting-enzyme inhibitors

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ABSTRACT

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide. Angiotensin-converting-enzyme inhibitors (ACEs) have a role in reducing malignant changes of the liver, and some of ACE inhibitors, such as captopril, inhibited angiogenesis and the growth of induced tumor. ACE inhibitor is associated with the suppression of the vascular endothelial growth factor (VEGF) at a clinically comparable dose, also markedly suppressed the hepato-carcinogenesis step. The present study aimed at evaluating the role of ACE inhibitors on the prognosis of HCC patients who have been treated by captopril.

Measurements of liver functions, serum Alfa fetoprotein (AFP) and VEGF of 40 Egyptian patients with HCC (23 patients with Child-Pugh Band, 17 patients with Child-Pugh C) compared with 8 normal individuals at pre- and post-administration.

There was statistically significant decrease of liver functions except serum albumin, serum AFP and VEGF in HCC patients at post administration compared with preadministration. In addition, at pre administration there was significant correlation of serum VEGF with albumin (r = - 0.379) and with serum AFP (r = 0.492) and at post administration with albumin (r = - 0.492) and with AFP concentration (r = 0.619). The prognostic value of serum AFP and VEGF was assessed by ROC curve showing an AUC of 0.689 and 0.907, respectively for identifying patients with HCC post administration of Captopril.

In conclusions the results indicated that ACE inhibitor significantly inhibits tumor growth and angiogenesis along with suppression of the serum VEGF and AFP levels. This may be used in the clinical trials as anti angiogenic agents against cancer, and may be applicable as an anti-cancer agent providing a new strategy for cancer therapy.

Key words: Angiotensin, Inhibitors, Vascular endothelial growth factor, hepatocellular carcinoma (HCC), prognosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the second leading cause of cancer-related deaths (Flores and Marrero, 2014). In Egypt, the prevalence of HCC is increasing during last years which has a high prevalence of hepatitis C virus (El-Aassar *et al.*, 2014). HCC is a highly aggressive disease because of its constantly increasing incidence and its poor prognosis owing to the lack of any effective treatment for the invasive and metastatic disease (Siegel *et al*., 2012; Llovet *et al*., 2003). Angiogenesis is a complex and critical process essential to support the growth of solid tumors could be inducing at the early stages of tumor formation and carcinogesis (Carmeli *et al*., 2003; Bergers *et al*., 2003). Angiotensin-converting-enzyme inhibitors (ACE), which

is a potent inhibitor of experimental HCC growth and angiogenesis, is associated with the suppression of the Vascular endothelial growth factor (VEGF) at a clinically comparable dose, also markedly suppressed the hepato-carcinogenesis step (Yoshiji *et al*., 2002).Captopril (D-3-mercapto-2-methylpropanoyl-L-proline) is an orally active competitive inhibitor of ACE (Materson and Preston, 1994). Presumably, because of the sulfhydryl group in its molecular structure; Captopril is a potent free radical scavenger and antioxidant (William and Agostino, 1993). Since ACE, inhibitor is used widely in clinical practice without serious side effects (Yoshiji *et al*., 2002) and statistically significantly positive correlation between serum level of VEGF and grade of HCC was recorded. Thus, assessment of this parameter with different stages of disease may be helpful in choosing the best treatment strategy, and indicate the antiangiogenic therapy may be useful (Talaat, 2010). The present study aimed to evaluating the effect of captopril as an ACE inhibitor on Egyptian HCC patients by measurements of serum AFPand VEGF.

PATIENTS AND METHODS

Patients

This study was approved by the ethic committees of the National Institute for Oncology in Damietta, from January, 2012 through December, 2014 and informed consent was obtained from all patients after full explanation for the purpose of the study. Group of 48Egyptian patients were invited to participate in the present study. The patients were divided into: 8 healthy subjects (mean age: 56.87±7.08 years;42 - 69 years) including 5 males and 3 females recruited into this group Forty patients with HCC (21 males and 19 females) diagnosed by physicians of National Institute for Oncology in Damietta (mean age : 58.58±8.47 years, range: 44-75 years). The diagnosis of HCC in those patients was carried out according to the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines (Bruix and Sherman, 2005).

They were divided to two classes: Twenty three subjects with Child-pugh B (12 males and 11 females) and Seventeen subjects with Child-pugh C (9 males and 8 females). Blood samples were collected by vein-puncture and sera were separated from the blood samples and were stored at -20 °C tell analyzed for tests required in this study. An oral administration of ACE inhibitor (CAPTOPRIL 50mg) per day for, duration of 3 months, to Egyptian patients with HCC.

Methods

Laboratory Tests

Blood samples were collected by venipuncture and tested for liver function tests (AST, ALT, alkaline phosphatase, total and direct bilirubin and serum albumin). Liver function tests were measured on an automated biochemistry analyzer (Hitachi 917; Roche Diagnostics, Mannheim, Germany).

Determination of Alpha-Fetoprotein (AFP)

BIOSOURCE AFP ELISA KIT is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle. The micro titer wells are coated with a monoclonal antibody directed towards a unique antigenic site on an AFP molecule. An aliquot of patient sample containing endogenous AFP is incubated in the coated well with enzyme conjugate, which is an anti-AFP antiserum conjugated with horseradish peroxidase. After incubation the unbound conjugate is washed off with water. The amount of bound peroxidase is proportional to the concentration of AFP in the sample. Having added the substrate solution, the intensity of

color developed is proportional to the concentration of AFP in the patient sample. The average absorbance values were calculated for each set of reference standards, controls and group samples. A standard curve was constructed by plotting the mean absorbance obtained from each reference standard against its concentration. The mean absorbance value was used for each sample to determine the corresponding concentration of AFP in ng/ml from the standard curve.

Measurement of Serum VEGF Level

Serum VEGF levels were quantitatively measured by a Human VEGF ELISA (Enzyme-Linked Immunosorbent Assay) kit designed to measure human VEGF concentration in serum by the method of (Kim *et al*., 1992; Ferrara *et al*.; 1991**).** Human VEGF ELISA kit is an in vitro enzyme-linked immunosorbent assay for the quantitative measurement of human VEGF in serum. This assay employs an antibody specific for human VEGF coated on a 96-well plate. Standards and samples are pipetted into the wells and VEGF present in a sample is bound to the wells by the immobilized antibody. The wells are washed and biotinylated antihuman VEGF antibody is added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed, a TMB substrate solution is added to the wells and color develops in proportion to the amount of VEGF bound. The Stop Solution changes the color from blue to yellow, and the intensity of the color is measured at 450 nm. Calculate the mean absorbance for each set of standards, controls and samples, and subtract the average zero standard optical density. Plot the standard curve on log-log graph paper or using Sigma plot software, with standard concentration on the x-axis and absorbance on the y-axis. Draw the best-fit straight line through the standard points.

Statistical Analysis

All statistical analyses were done by a Statistical Package for the Social Sciences (SPSS); version20.0 (SPSS Inc., Chicago, IL, USA) under Microsoft Windows 7. Descriptive results were expressed as mean ± SD and range or number (percentage) of patients with a condition. Differences in continuous variables were assessed using Student's t-test or analysis of variance (ANOVA) and X^2test for categorical variables. All tests were two-tailed and statistical significance was assessed at the 0.05 level. The prognostic value was assessed by calculating the area under the receiver-operating characteristic (ROC) curves.

RESULTS

Liver functions Tests

Atpre administration of Captopril, patients with HCC had high levels of liver functions (AST, ALT, alkaline phosphatase, total and direct bilirubin) except serum albumin had low levels in comparison with controls**.** Moreover**,** in patients with HCC, there was significant decrease in the levels of liver functions (AST, ALT, alkaline phosphatase, total and direct bilirubin) except serum albumin there was significant increase at post-treatment compared with pre-treatment**.** In addition, there was significant decrease in the levels of liver functions (AST, ALT, alkaline phosphatase, total and direct bilirubin) except serum albumin there was significant increase at post- treatment compared with pre-treatment in HCC patients with Child-Pugh B and C (Table 1).

The levels of serum AFP and VEGF at pre and post administration of Captopril

In patients with HCC with Child-Pugh B, there was an extremely high

significant decrease ($p < 0.0001$) in the levels of serum AFP (644.30±186.00 U/L) and serum VEGF; 345.00±79.84pg/L at post administration of Captopril in comparison with pre administration of Captopril (1075.74±356.10 U/L) and (562.13±108.64 pg/L), respectively. The same in patients with HCC with Child-Pugh C, there was an extremely high significant decrease ($p < 0.0001$) in the levels of serum AFP (2955.18±1627.48 U/L) and serum VEGF; 474.18±106.18 pg/L at post administration of Captopril in comparison with pre administration of Captopril (4563.76 ± 2172.68 U/L) and (855.24 ± 265.26pg/L), respectively. In addition, At pre-administration of Captopril, there was statistically an extremely significant difference ($P<0.0001$) in serum AFP and VEGF between HCC patients with Child-Pugh B and Child-PughC andatpost-treatment, there was statistically an extremely significant difference ($P<0.0001$) of serum AFP and VEGF between HCC patients with Child-Pugh B and Child-Pugh C (Table 2).

Relation of serum VEGF with biomarkers in HCC patients

In patients with HCC pre administration of Captopril, there was no significant correlation for serum VEGF with ALT, total bilirubin, D. Bilirubin but there was significant correlation between serum VEGF concentrations with AST ($r = 0.368$; $P < 0.01$), serum ALP ($r = 0.371$; $p < 0.01$), serum albumin ($r = - 0.379$; $P = 0.01$) and with serum AFP concentration ($r = 0.492$; $p < 0.001$) (Fig. 1A-B). In addition, in patients with HCC post administration of Captopril, there was no significant correlation for serum VEGF with ALT, ALP, total bilirubin and D. Bilirubin but there was significant correlation with AST ($r = 0.462$; $P < 0.01$), serum albumin ($r = - 0.492$; $P = 0.01$) and with AFP concentration ($r = 0.619$; $p < 0.0001$)(Fig. 1C-D).

Performance Characteristics of serum AFP and VEGF

The prognostic value of serum AFP was assessed in the estimation group by ROC curve showing an AUC of 0.689 and $p < 0.001$ for identifying patients with HCC post administration of Captopril (Fig. 2A).In addition, the prognostic value of this serum VEGF was assessed in the estimation group by ROC curve showing an AUC of 0.907 and $p < 0.0001$ for identifying patients with HCC post administration of Captopril (Fig. 2B).

DISCUSSION

One of the reasons for the poor prognosis of HCC its high rates of recurrence, even after the curative therapy, is due to intrahepatic metastasis or multi-centric development of each respective neoplasm clone (Minguez *et al*., 2009). Preclinical data suggested that significant HCC growth is dependent on angiogenesis and an increase in tumour dimension may induce vascular endothelial cell proliferation (Montella *et al*., 2008).Because inhibition of angiogenesis is considered promising approach for cancer therapy, efforts are being directed at overcoming tumor angiogenesis worldwide (Ferrara and Alitalo, 1999). ACE inhibitors demonstrated significant inhibitory effects on experimental murine liver fibrosis and HCC development (Yoshiji, 2009; Jonsson *et al*., 2001).The relation between the ACE inhibitor and VEGF expression in the tumor cells need more examination. In the present study, we examined the effect of type of ACE inhibitors, captopril, on tumor development and angiogenesis in patients with HCC. The evaluated AST, ALT, ALP and bilirubin had higher values in HCC patients but serum albumin had lower levels compared to controls. In addition, AST,

ALT, ALP and bilirubin had lower values at post than pre administration but serum albumin had higher levels at post than pre. ALT and AST are sensitive indicators of hepatocellular injury and in hepatocyte cytoplasm AST is more abundant than ALT. These aminotransferases may be increased in patients presenting with cirrhosis, chronic hepatitis, alcoholic hepatitis, acute viral hepatitis and HCC (Pratt and Kaplan, 2000). Liver ALP, found on canalicular surfaces, is raised in any condition of biliary obstruction (intrahepatic and extra-hepatic). In hepatocyte injury, ALP is often normal or marginally elevated. This feature is used as a guide to differentiate liver parenchymal disease from biliary dysfunction (Green and Flamm, 2002).The serum bilirubin levels more than 1mg/dL suggest liver diseases and levels above 1.4mg/dL indicate abnormal laboratory liver tests (Johnston, 1999). In viral hepatitis, hepatocellular damage, toxic or ischemic liver injury higher levels of serum conjugated bilirubin is seen (Thapa and Anuj, 2007). Albumin synthesis is regulated by nutritional status, osmotic pressure, systemic inflammation, and hormone concentration in the blood (Kang, 2013). Measurement of serum albumin levels is useful in chronic liver disease and is a component of grading Liver Disease Score (Green and Flamm, 2002).Detections of circulating biomarkers are useful to find tumor at an early stage or monitor metastasis after postoperative treatment (Wang *et al*., 2014).AFP is not only serves as a valuable tumor maker for patients with liver cancer, but it also possess important regulatory effect for several important biological processes such as cell differentiation, proliferation and apoptosis in embryogenesis and tumor growth (Mizejewski and MacColl, 2003). AFP could regulate cell proliferation and apoptosis, and thus plays a role in liver cancer formation (Li *et al*., 2004).In the present study, there was a statistically significant difference in the level of AFP in normal individuals and patients with HCC. In addition, AFP had lower levels at post than pre administration. The level of AFP increases in HCC patients due to the re-expression of the related gene, which is usually repressed in adult subjectsbut AFP is not elevated in all patients with HCC (Pontisso *et al*., 2006; Personeni *et al*., 2012). Many anti-angiogenic compounds are being developed, most of which target VEGF and/or its receptors. It is necessary to establish whether VEGF expression is a prognostic marker in HCC (Zhan *et al*., 2013).VEGF-driven pathway has been demonstrated to play a major role in tumor angiogenesis (Scartozzi *et al.*, 2014).Therefore, the concentration of circulating VEGF is included as a candidate prognostic marker for HCC, especially in patients with advanced disease. In the present study, there was significant difference in the serum level of VEGF in normal individuals and patients with HCC. In addition, levels of serum VEGF at post lower than at pre administration. A retrospective cohort study of 5207 patients receiving ACE inhibitor or other hypertensive drugs with a 10-year follow-up has shown that ACE inhibitor may decrease the incidence of adult cancer and fetal cancer (Lever *et al*., 1998).VEGF is the major mediator of angiogenesis in HCC, and several studies have correlated VEGF concentrations with the prognosis of patients who have advanced HCC (Yoshiji *et al*., 2002; Llovet *et al*., 2012).

In conclusion, changes in serum VEGF concentrations during treatment are dynamic in patients with advanced HCC, and an observed decrease in the serum VEGF concentration. Our results have potentially important clinical implications for physicians and may influence their

decisions regarding a treatment strategy for advanced HCC in individual patients.

Conflict of interest

The authors declared that there iconflict of interest.

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Table 1. Laboratory data of controls and HCC patients at pre- and post- captopril administration.

Variable [a]	Controls	Pre-administration	Post-administration	P value [b]
ALT (U/L)	27.38±3.06	62.63±25.19	40.75±7.80	<0.0001
Range	22.80-30.60	39.00-165.00	36.60-84.00	
AST (U/L)	30.42±1.57	93.57±49.72	45.60±5.68	< 0.0001
Range	28.60-33.00	45.00-274.00	39.00-60.00	
ALP (U/L)	55.6±13.2	220.90±150.00	120.55±21.79	< 0.0001
Range	40.2-76.8	100.00-812.00	96.0-200.0	
S. Albumin (g/dl)	3.94±0.43	3.41±0.23	3.72±0.37	< 0.0001
Range	3.20-4.60	2.60-3.80	3.20-4.60	
T. Bilirubin (mg/dl)	0.60±0.25	2.25±1.14	1.43±0.35	< 0.0001
Range	0.21-0.88	1.13-7.20	1.09-2.60	
D. Bilirubin (mg/dl)	0.16±0.03	1.10±0.79	0.53±0.35	< 0.0001
Range	0.12-0.20	0.26-2.58	0.23-1.56	
AFP (U/L)	6.75±2.57	2558.15±2248.8	1626.43±1563.53	< 0.0001
Range	3.17-10.00	622.0-8150.0	375.0-7200.0	

[a] Variables were expressed as mean ± SD. Reference values: aspartate aminotransferase (AST) (male up to 37 U/L, female up to 31 U/L); alanine aminotransferase (ALT) (male up to 41 U/L, female up to 31 U/L); alkaline phosphatase (ALP) 22-92 U/L; serum albumin 3.8-5.4 g/dL; total bilirubin up to 1 mg/dL; direct bilirubin up to 0.25 mg/dL and Alpha fetoprotein (AFP) up to 10 U/L. [b]p value: $p > 0.05$ non-significant; $p < 0.05$ significant, $p < 0.01$ highly significant and $p < 0.0001$ extremely high significant.

Table 2. Laboratory data of Child-pugh score of HCC patients at pre- and post- captopril administration.

Variable [a]	Child-Pugh B(n =23)			Child-Pugh C(n = 17)		
	Pre	Post	P value [b]	Pre	Post	P value [b]
ALT (U/L)	53.48±9.81	39.48±3.42	*< 0.0001*	75.00±33.65	42.41±11.26	*<0.001*
Range	42.0-87.0	36.0-48.0		39.0-165.0	36.0-84.0	
AST (U/L)	73.08±22.32	44.35±5.31	*< 0.0001*	121.29±62.6	47.29±5.88	*<0.0001*
Range	45.0-139.0	39.0-57.0		52.0-274.0	39.0-60.0	
ALP (U/L)	167.1±44.6	119.6±16.2	*< 0.0001*	293.7±205.7	133.6±26.0	*<0.01*
Range	106.0-277.0	97.0-146.0		100.0-812.0	96.0-200.0	
Albumin (g/dl)	3.43±0.18	3.77±0.41	*< 0.001*	3.41±0.31	3.65±0.30	*<0.05*
Range	3.20-3.80	3.20-4.60		2.60-3.80	3.30-4.50	
T. Bilirubin (mg/dl)	2.17±0.84	1.43±0.32	*< 0.0001*	2.36±1.47	1.43±0.38	*<0.01*
Range	1.20-4.50	1.10-2.60		1.10-7.20	1.00-2.60	
D. Bilirubin (mg/dl)	1.00±0.74	0.46±0.32	*< 0.01*	1.22±0.88	0.62±0.37	*<0.05*
Range	0.26-2.80	0.23-1.22		0.26-3.50	0.24-1.50	
AFP (U/L)	1075.7±356.	644.3±186.0	*< 0.0001*	4563.76±2172.68	2955.2±1627	*< 0.05*
Range	622.0-1826.0	375.0-983.0		1216.0-8150.0	956.1-7200.0	
VEGF (pg/L)	562.1±108.6	345.0±79.8	*< 0.0001*	855.2±265.2	474.2±106.2	*< 0.0001*
Range	320.0-764.0	210.0-475.0		540.0-1550.0	302.0-675.0	

[a] Variables were expressed as mean ± SD. Reference values: aspartate aminotransferase (AST) (male up to 37 U/L, female up to 31 U/L); alanine aminotransferase (ALT) (male up to 41 U/L, female up to 31 U/L); alkaline phosphatase (ALP) 22-92 U/L; serum albumin 3.8-5.4 g/dL; total bilirubin up to 1 mg/dL; direct bilirubin up to 0.25 mg/dL.[b]p value: $p > 0.05$ non-significant; $p < 0.05$ significant, $p < 0.01$ highly significant and $p < 0.0001$ extremely high significant.

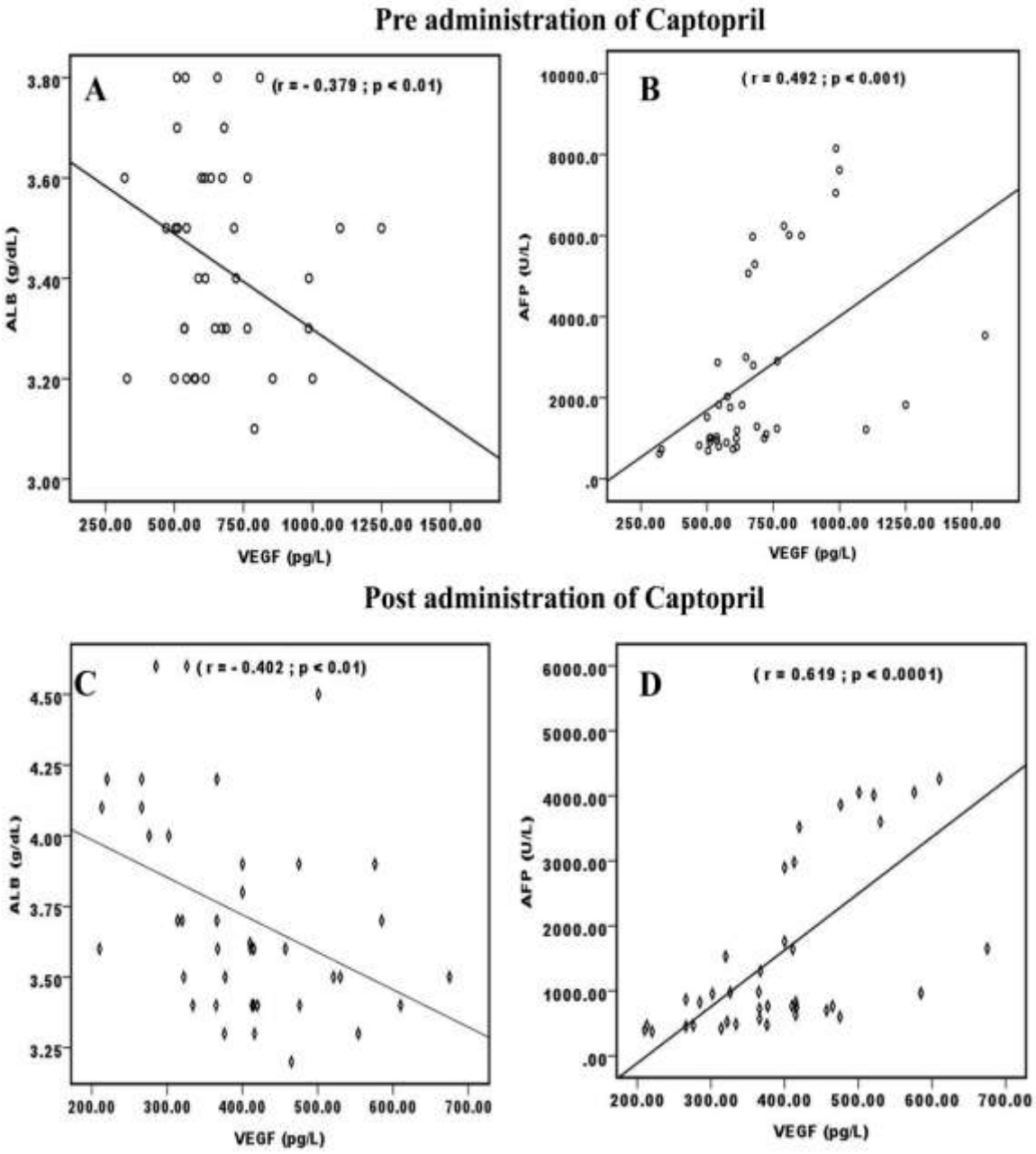

Fig. 1: Correlation of serum VEGF with laboratory parameters in HCC patients. A and B. Correlation of serum VEGF with laboratory parameters in pre administration HCC patients. (A) There was significant correlation with serum albumin (r = - 0.379; P = 0.01).(B)There was strong significant correlation with serum AFP concentration (r = 0.492; p < 0.001).C and D. Correlation of serum VEGF with laboratory parameters in post administration HCC patients.(C)There was significant correlation with serum albumin (r = - 0.492; P = 0.01). (D)There was strong significant correlation with serum AFP concentration (r = 0.619; p < 0.0001).

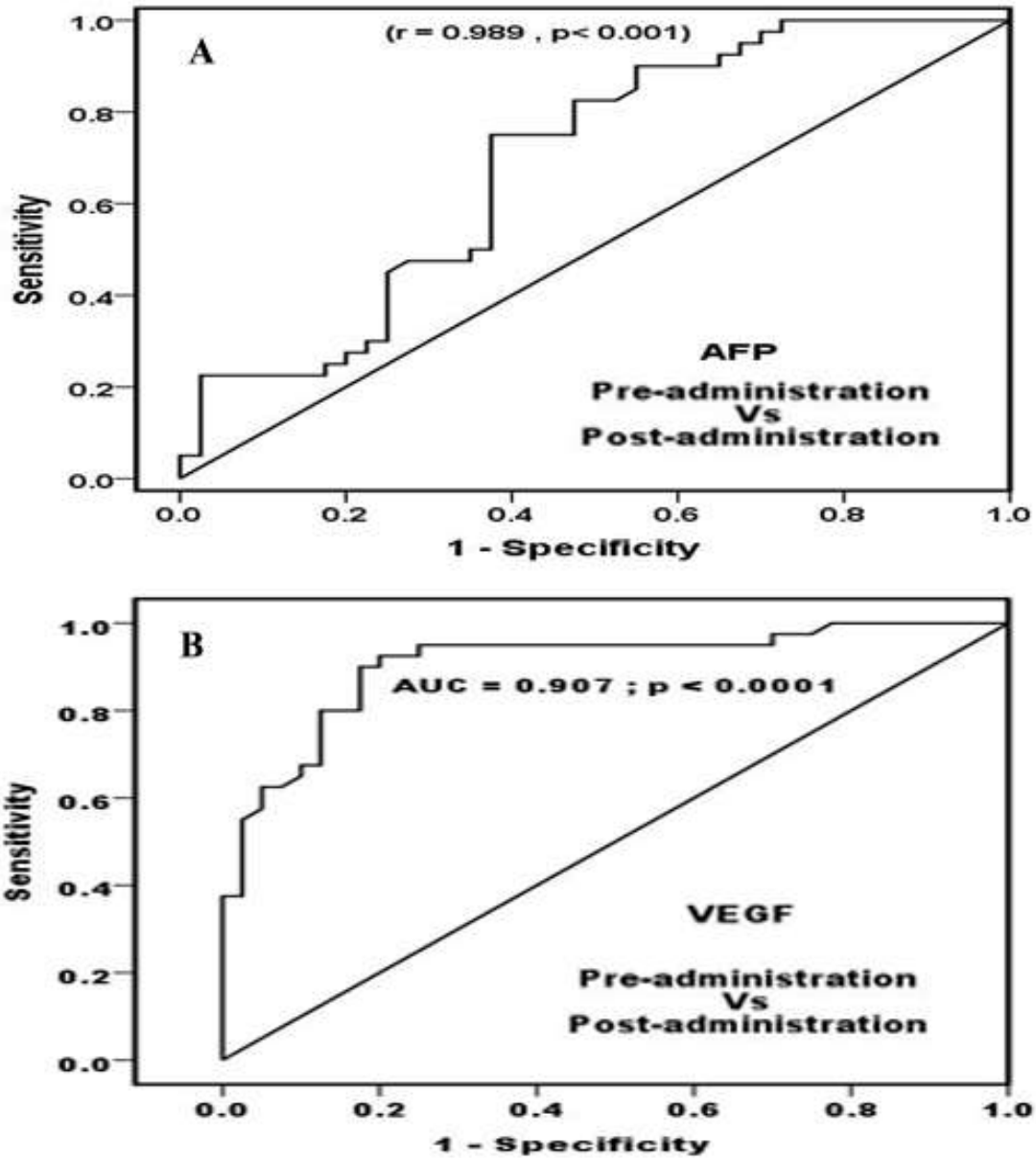

Fig. 2: Areas under receiver-operating characteristic curve (AUC) inpatients with HCC for (A) AFP for predicting post administration for captopril, with an AUC of 0.689. (B) VEGF for predicting post administration for captopril with an AUCof 0.907. Each point on the ROC plot represents a sensitivity/specificitypair corresponding to a particular decision threshold. An AUC of 1.0 ischaracteristic of an ideal test whereas an AUC of 0.5 or less indicates atest of no diagnostic value.

REFERENCES

Aleem, E.; Elshayeb, A.; Elhabachi, N.; Mansour A.R.; Gowily A.; and Hela A. (2012). Serum IGFBP-3 is a more effective predictor than IGF-1 and IGF-2 for the development of hepatocellular carcinoma in patients with chronic HCV infection. Oncol. Lett., 3(3):704-712.

Bergers, G. and Benjamin, L.E. (2003). Tumorigenesis and the angiogenic switch. Nat Rev Cancer., 3:401-410.

Bruix, J. and Sherman, M. (2005). Management of hepatocellular carcinoma. Hepatol., 42:1208–1236.

Carmeliet, P. (2003). Angiogenesis in health and disease. Nat. Med., 9:653–660.

El-Aassar, M.R.; Hafez, E.E.; El-Deeb, N.M. and Fouda, M.M. (2014). Microencapsulation of lectin anti-cancer agent and controlled release by alginate beads, biosafety approach.Int. J. Biol. Macromol., 69C:88-94.

Ferrara, N.; Houck, K.A.; Jakeman, L.B.; Winer, J.; Leung, D.W. (1991). The vascular endothelial growth factor family of polypeptides. J.Cell. Biochem., 147: 211-8.

Ferrara, N. and Alitalo, K. (1999). Clinical applications of angiogenic growth factors and their inhibitors. Nat. Med., 5: 1359–1364.

Ferrara, N. and Davis-Smyth, T. (1997). The biology of vascular endothelial growth factor. Endocr. Rev., 18: 4–25,.

Flores, A. and Marrero, J.A. (2014). Emerging Trends in Hepatocellular Carcinoma: Focus on Diagnosis and Therapeutics. Clin. Med. Insights Oncol., 8:71-76.

Folkman, J. (1995). Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat. Med., 1: 27–31.

Green, R.M. and Flamm, S. (2002). AGA Technical Review on the Evaluation of Liver Chemistry Tests. Gastroenterol., 123(4):1367–1384.

Johnston, D.E. (1999). Special Considerations in Interpreting Liver Function Tests. Am. Fam. Physician, 59(8):2223–2230.

Jonsson, J.R. ; Clouston, A.D.; Ando, Y.; Kelemen, L.I.; Horn, M.J.; Adamson, M.D.; Purdie, D.M. and Powell, E.E. (2001). Angiotensin-converting enzyme inhibition attenuates the progression of rat hepatic fibrosis. Gastroenterol., 121:148–155.

Kang, K.S. (2013). Abnormality on liver function test. Pediatr Gastroenterol. Hepatol. Nutr., 16(4):225-232.

Kim, K.J.; Li, B.; Houck, K.; Winer, J. and Ferrara, N. (1999). The vascular endothelial growth factor proteins: identification of biologically relevant regions by neutralizing monoclonal antibodies. Growth Factors, 27: 53-64.

Lever, A.F.; Hole, D.J.; Gillis, C.R.; McCallum, I.R.; McInnes, G.T.; MacKinnon, P.L.; Meredith, P.A.; Murray, L.S.; Reid, J.L. and Robertson, J.W. (1998). Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? Lancet, 352: 179–184,.

Li, M.; Li, P.F.; Chen, Q.; Du, G.G.; and Li, G. (2004). Alpha-fetoprotein stimulated the expression of some oncogenes in human hepatocellular carcinoma Bel 7402 cells. World J. Gastroenterol., 10(6): 819–824.

Llovet, J.M. and Bruix, J. (2008). Molecular targeted therapies in hepatocellular carcinoma. Hepatol., 48:1312–1327.

Llovet, J.M.; Burroughs, A. and Bruix, J. (2003). Hepatocellular carcinoma. Lancet, 362:1907–1917.

Llovet, J.M.; Pena, C.E.; Lathia, C.D.; Shan, M.; Meinhardt, G.and Bruix, J. (2012). Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma.Clin Cancer Res., 18:2290-3000.

Materson, B.J. and Preston, R.A. (1994). Angiotensin-converting enzyme

inhibitors in hypertension. Arch. Intern. Med., 154:513–523.

Minguez, B.; Tovar, V.; Chiang, D.; Villanueva, A. and Llovet, J.M. (2009). Pathogenesis of hepatocellular carcinoma and molecular therapies. Curr Opin Gastroenterol.,25: 186-194.

Mizejewski, G.; MacColl, R. (2003). Alpha-fetoprotein growth inhibitory peptides: potential leads for cancer therapeutics. Mol. Cancer Ther., 2: 1243–1255.

Montella, L.; Addeo, R.; Caraglia, M.; Faiola, V.; Guarrasi, R.; Vincenzi, B.; Palmeri, A.; Capasso, E.; Nocera, V, Tarantino, L.; Ariete, M.; Martorelli, A. and Del Prete, S. (2008). Vascular endothelial growth factor monitoring in advanced hepatocellular carcinoma patients treated with radiofrequency ablation plus octreotide: a single center experience. Oncol. Rep., 20:385–90.

Personeni, N.; Bozzarelli, S.; Pressiani, T.; Rimassa, L.; Tronconi, M.C.; Sclafani, F.; Carnaghi, C.; Pedicini, V.; Giordano, L. and Santoro, A. (2012). Usefulness of alpha-fetoprotein response in patients treated with sorafenib for advanced hepatocellular carcinoma. J. Hepatol., 57:101-107.

Pontisso, P.; Quarta, S.; Caberlotto, C.; Beneduce, L.; Marino, M.; Bernardinello, E.; Tono, N.; Fassina, G.; Cavalletto, L.; Gatta, A. and Chemello, L. (2006). Progressive increase of SCCA IgM immune complexes in cirrhotic patients is associated with development of hepatocellular carcinoma. Int. J. Cancer, 119(4): 735–740.

Pratt, D.S. and Kaplan, M.M. (2000). Evaluation of Abnormal Liver-Enzyme Results in Asymptomatic Patients. NEJM., 342(17):1266–1271.

Scartozzi, M.; Faloppi, L.; SvegliatiBaroni, G.; Loretelli, C.; Piscaglia, F.; Iavarone, M.; Toniutto, P.; Fava, G.; De Minicis, S.; Mandolesi, A.; Bianconi, M.; Giampieri, R.; Granito, A.; Facchetti F, Bitetto D, Marinelli, S.; Venerandi, L.; Vavassori, S.; Gemini, S.; D'Errico, A.; Colombo, M.; Bolondi, L.; Bearzi, I.; Benedetti, A.; Cascinu, S. (2014). VEGF and VEGFR genotyping in the prediction of clinical outcome for HCC patients receiving sorafenib: the ALICE-1 study. Int. J. Cancer, 135(5):1247-56.

Siegel, R.; Naishadham, D. and Jemal, A. (2012). Cancer statistics, 2012. CA Cancer J. Clin., 62:10–29.

Talaat, R.M. (2010). Soluble angiogenesis factors in sera of Egyptian patients with hepatitis C virus infection correlation with disease severity.ViralImmunol, 23(2):151-7.

Tamesa, T.; Iizuka, N.; Mori, N. et al. (2009). High serum levels of vascular endothelial growth factor after hepatectomy are associated with poor prognosis in hepatocellular carcinoma. Hepatogastroenterology. 56:1122-1126.

Thapa, B.R. and Anuj, W. (2007). Liver Function Tests and their Interpretation. Ind. J. Pediatr., 74: 663-671.

Volpert, O.V.; Ward, W.F.; Lingen, M.W.; Chesler, L.; Solt, D.B.; Johnson, M. D.; Molteni, A.; Polverini, P.J. and Bouck, N.P. (1996). Captopril inhibits angiogenesis and slows the growth of experimental tumors in rats. J. Clin. Invest., 98: 671–679,.

Wang, L.; Yao, M.; Dong, Z.; Zhang, Y. and Yao, D. (2014). Circulating specific

biomarkers in diagnosis of hepatocellular carcinoma and its metastasis monitoring.Tumour Biol., 35(1):9-20.

William, F.W. and Agostino, M. (1993). Captopril as a chemopreventive agent. Free Patent Online, Pt no.5192524.

Yamaguchi, R.; Yano, H.; Iemura, A.; Ogasawara, S.; Haramaki, M. and Kojiro, M. (1998). Expression of vascular endothelial growth factor in human hepatocellular carcinoma. Hepatology, 28: 68-77.

Yoshiji, H.; Kuriyama, S.; Yoshii, J. et al. (2002). Synergistic effect of basic fibroblast growth factor and vascular endothelial growth factor in murine hepatocellular carcinoma. Hepatol., 35:834-842.

Yoshiji, H. (2009). Combination of vitamin K2 and angiotensin-converting enzyme inhibitor ameliorates cumulative recurrence of hepatocellular carcinoma. J. Hepatol., 51:315–321.

Zhan, P.; Qian, Q. and Yu, L.K. (2013). Serum VEGF level is associated with the outcome of patients with hepatocellular carcinoma: a meta-analysis. Hepatobil. Surg. Nutr., 2 (4):209-15.

تأثير عامل نمو بطانة الأوعية الدموية على تشخيص مرضى السرطان الكبدي المعالَج باستخدام مثبطات اللانزيم المحوللانجيوتنسين

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المستخلص

سرطان الخلايا الكبدية هو السرطان السادس الأكثر شيوعا والسبب الرئيسي الثالث للوفيات في جميع انحاء العالم. مثبطات الانزيم المحول للأنجيوتنسين لها دور في الحد من التغيرات الخبيثة في الكبد، وبعض مثبطات الانزيم المحول للأنجيوتنسين مثل الكابتوبريل يعمل على تثبيط كل من عملية تكوين الاوعية الدموية ونمو الورم المستحث.مثبطات الانزيم المحول للأنجيوتنسين ترتبط مع تثبيط عامل نمو بطانة الاوعية الدموية في الدم وذلك في جرعات قابلة للمقارنة طبيا. أيضا تثبيط بشكل ملحوظ لخطوة تكوين الخلايا السرطانية الكبدية. استهدف ت هذ الدراسة تقييم دور مثبطات الإنزيم المحول للأنجيوتنسين في تشخيص مرضى سرطان الكبد الذين اعطوا كابتوبريل.

تم قياس مصل الدم لتقييم وظائف الكبد والالفا فيتوبروتين وعامل نمو بطانة الأوعية الدموية لأربعين مريض مصري مصاب بسرطان الخلايا الكبدية منهم 23 مريض من الحالة التشخيصية بي وأيضا 19 مريض من الحالة التشخيصية سي مقارنة بـ 8 من الأشخاص الاصحاء قبل وبعد إعطاء كابتوبريل. وقد اتضح من النتائج ان هناك انخفاض ذو دلالة إحصائية من وظائف الكبد باستثناء الالبيومين في مصل الدم، وأيضا انخفاض مستوي المصل للألفا فيتوبروتين وعامل نمو بطانة الأوعية الدموية قبل وبعد إعطاء كابتوبريل لمرضي سرطان الخلايا الكبدية. بالإضافة إلى ذلك وجد ان هناك ارتباط ملحوظ مابين عامل نمو بطانة الأوعية الدموية والالبيومين في مصل الدم (r=-0.379)، وكذلك مع الالفا فيتو بروتين في مصل الدم (r=0.492) وذلك قبل إعطاء الكابتوبريل. وأيضا وجد ان هناك ارتباط ملحوظ مابين عامل نمو بطانة الأوعية الدموية والالبيومين في مصل الدم (r=-0.492)، وكذلك مع الالفا فيتوبروتين في الدم (r=0.619) وذلك بعد إعطاء الكابتوبريل. وأيضا وجد ان القيمة التنبؤية لمصل الدم للالفا فيتو بروتين وعامل نمو بطانة الاوعية الدموية والتى تم تقييمها بواسطة منحنى روك تظهر بواسطة المنطقة التي تحت المنحني على التوالى من 0.689 و 0.907 فى تحديد مرضى سرطان الخلايا الكبدية بعد اعطائهم كابتوبريل. كما امكن استنتاج ان مثبطات الإنزيم المحول للانجيوتنسين بشكل ملحوظ تثبط نمو الورم وعملية تكوين الاوعية الدموية الي جانب تثبيط لمستويات مصل الدم للالفا فيتو بروتين وعامل نمو بطانة الاوعية الدموية. ويمكن استخدام هذا في التجارب السريرية كعوامل مضادة لتكوين الأوعية الدموية كمثبطات لنمو الخلاياالسرطانية، ويمكن تطبيقه كعامل مضاد للسرطان وبالتالي يوفر استراتيجية جديدة لعلاج الأورام الخبيثة.