The Diagnostic Value of Serum Vascular Endothelial Growth Factor as a Predictor of Hepatocellular Carcinoma in Patients with HCV related Liver Cirrhosis

Thesis

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List of Abbreviations

AAT .....Alpha-1 Antitrypsin

ACS .....Anorexia-cachexia syndrome

AFP .....Alfa feto protien

AFP-L3.....Alpha-fetoprotein Lens culinaris agglutiin 3

AFU .....α-l-fucosidase

ALS.....Amyotrophic lateral sclerosis

ALT .....Alanine aminotransferas.

Ang2.....Angiopoietin-2

ARE.....Antioxidant Response Element

AST .....Aspartate aminotransferase

BCL-2 .....B-cell lymphoma 2

BCLC .....Barcelona Clinic Liver Cancer

CEPs.....Circulating bone marrow–derived endothelial precursor cells

CLIP .....Cancer of Liver Italian Program

CT .....Computed tomography.

CUPI.....Chinese University Prognostic Index

DCP .....Des gamma carboxy prothrombin

ECM .....Extracellular matrix

EGFR.....Epidermal growth factor receptor

ERK.....Extracellular signal-regulated kinase

EUS .....Endoscopic ultra sonography

FLK-1 .....Fetal liver kinase

FLT-1 .....Fms-like tyrosine kinase

GDP.....Guanosine 5'-diphosphate

List of Abbreviations (Cont.)

GGT.....Gamma-glutamyl transpeptidase
GP73 .....Golgi protein 73
GPC3 .....Glypican-3
GPI.....Glycosyl phosphatidyl inositol
HBe Ag.....Hepatitis B e antigen
HBsAg .....Hepatitis B surface antigen.
HBV.....Hepatitis b virus
HCC.....Hepatocellular carcinoma
HCV.....Hepatitis c virus
HIF .....Hypoxia-inducible factor
HIV.....Human immune deficiency virus
HSC.....Hepatic stellate cell
HSP .....Heat shock protien
HTA gene .....Hepatoma-associated gene
hTERT.....Human telomerase reverse transcriptase
ICC.....Cholangiocarcinoma
IFN.....Interferon
IFP .....Interstitial fluid pressure
IL-1 .....Interlukin-1
INH.....Isoniazid
INR.....International normalized ratio
IOUS.....Intra operative ultrasonography
JIS.....Japan Integrated Staging score
KDR .....Kinase insert domain receptor
LFT.....Liver function tests

List of Abbreviations (Cont.)

MAP Kinase.....Mitogen activated protien kinase

MEK .....Mitgen-activated protein kinase

MELD .....Model for endstage liver disease

MHC-1.....Major histocompatibility complex class 1

miRNA.....micro RNA

MMPs .....Matrix metalloproteinases

MRI .....Magnetic resonance imaging.

m-RNA.....Messenger RNA

MSCT .....Multi-Slice CT

M-TOR.....Mammalian target of rapamycin

NAFLD.....Nonalcoholic fatty liver disease

NASH.....Nonalcoholic steatohepatitis

NF-κB.....Nuclear factor kappa-light-chain-enhancer of activated B cells

NK cells.....Natural killer cells

NRF .....Nuclear factor erythroid related factor

PAF .....Platelet activating factor

PAI .....Percutaneous Acetic Acid Injection

PAT .....Parenteral anti Schistosomal therapy

PBC .....Primary biliary cirrhosis

PDGF.....Platelet derived growth factor

PEI .....Percutaneous Ethanol Injection

PENT pathway .....Pentose phosphate pathway

PGA.....Gamma-glutamyl transpeptidase activity, and serum apolipoprotein A1 concentration index

List of Abbreviations (Cont.)

PI3K ..... Phosphoinositide 3-kinase

PIVKA II ..... Prothrombin induced by Vitamin K Absence II

PLGF ..... Placental growth factor

PSC ..... Primary sclerosing cholangitis

PT ..... Prothrombin time

PUO ..... Pyrexia of unknown origin

PVT ..... Portal vein thrombosis

PZQ ..... Praziquantel

RAF-1 ..... Rapidly Accelerated Fibrosarcoma

RCC ..... Renal cell cancer

RFA ..... Radiofrequency abalation.

ROS ..... Called reactive oxygen species

ROS ..... Reactive oxygen species

SCCA ..... Squamous cell carcinoma antigen

SCCA-IgM IC ..... Squamous cell carcinoma antigen-immunoglobulin M immune complex

TAC ..... Trans arterial chemotherapy

TACE ..... Transarterial chemoembolization

TAE ..... trans arterial embolization

TAG-72 ..... Tumor associated glycoprotein

TE ..... Transient elastography

TGF ..... Transforming growth factor

TIMPs ..... Tissue inhibitors of metalloproteinases

TKI ..... Tyrosine kinase inhibitor

List of Abbreviations (Cont.)

TKR.....Tyrosine kinase receptor

TLR4 .....Toll-like receptor -4

TLS.....Tuomr lysis syndrome

TNF .....Tumour necrosis factor

TNM .....Tumor-node-metastasis

TRAIL.....Tumor necrosis factor–related apoptosis-inducing ligand

US .....Ultrasonography

VEGF.....Vascular endothelial growth factor

VEGF.....Vascular Endothelial Growth Factor Receptors

Vil1 .....Villin1

ZAG .....Zinc alfa 2 glycoprotien

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is considered one of the major causes of end-stage liver disease including cirrhosis and hepatocellular carcinoma. HCV infects more than 170 million people worldwide ***(Nelson et al., 2011).***

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide and is associated with the second lowest 5-year survival rate of all tumor types. Despite some advances in early diagnosis and therapeutic strategies, HCC prognosis remains poor. Therefore, the identification of a novel marker correlating with the clinic pathological features and prognosis is highly desirable ***(Jemal et al., 2010).***

Long as HCC most commonly appears in a patient with chronic viral hepatitis (hepatitis B or hepatitis C, 20%) or/and with cirrhosis (about 80%). These patients commonly undergo surveillance with ultrasound due to the cost-effectiveness. In patients with a higher suspicion of HCC (such as rising alpha-fetoprotein and des-gamma carboxyprothrombin levels), the best method of diagnosis involves a Triphasic CT scan of the abdomen using intravenous contrast agent and three-phase scanning (before contrast administration, immediately after contrast administration, and again after a delay) with the key characteristics on CT which are hypervascularity in the arterial

phase scans, washout or de-enhancement in the portal and delayed phase studies. A biopsy is not needed to confirm the diagnosis of HCC if certain imaging criteria are met ***(Kaido et al., 2011).***

An alternative to a CT imaging study would be the MRI. MRI's are more expensive and not as available because fewer facilities have MRI machines. More important MRI are just beginning to be used in tumor detection and fewer radiologists are skilled at finding tumors with MRI studies when it is used as a screening device. Mostly the radiologists are using MRIs to do a secondary study to look at an area where a tumor has already been detected. MRI's also use contrast agents. One of the best for showing details of liver tumors is very new: iron oxide nano-particles appears to give better results. The latter are absorbed by normal liver tissue, but not tumors or scar tissue ***(Tanaka et al., 2012).***

Several studies have also suggested a relationship between the progression of chronic liver disease and hepatocarcinogenesis. Chronic inflammation in the cirrhotic liver induces architectural and functional changes that result in hypoxia, one of the most potent stimuli for angiogenesis. Angiogenesis is essential for carcinogenesis and is induced directly by vascular endothelial growth factor (VEGF), leading to tumor growth and metastasis ***(Wu, 2006).***

VEGF is a primary driving force for both physiological and pathological angiogenesis. VEGF expression is correlated with tumor vascularity ***(Semela and Dufour, 2005).***

The vascular endothelial growth factor gene family, which encodes five polypeptide growth factors, VEGF-A, -B, -C, -D, and placenta like growth factor (PLGF), is particularly important because of its angiogenic and lymphangiogenic properties that promote the growth and metastasis of neoplasms. VEGF-C is regarded as the most efficient factor in regulating lymph angiogenesis ***(Li et al., 2011).***