The Diagnostic Value of Serum Golgi protein 73 (GP 73) as a Biomarker for Hepatocellular Carcinoma in Patients with HCV related Liver Cirrhosis

Thesis

A Study Submitted for the Partial Fulfillment of the Master Degree ***in Internal Medicine***

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Abstract

Hepatocellular carcinoma is one of the most common malignancies worldwide and the most common primary malignant tumor of the liver.Diagnosis of HCC at earlier stages improves patient outcomes.Currently, the most commonly used methods forscreening and diagnosing HCC are ultrasound imagingand serum α-fetoprotein (AFP) concentration measurements, but the diagnostic value of AFP is recently challenged due to its low sensitivity and specificity.

Golgi protein 73 (GP73, also known as Golph2), is a 400 aminoacid, 73-kDa resident Golgi-specific membrane protein expressed bybiliary epithelial cells in normal liver, and its expression isincreased markedly in chronic liver diseases, especially in HCC cells.It is responsible for decreasing the surface area of the Golgi apparatus and hence maintaining its integrity during cellular stress and many studies identified it as a potential biomarker for HCC. The study was conducted upon 75 subjects who were divided into three groups: group I included 25 patients with liver cirrhosis and hepatocellular carcinoma , group II included 25 patients with HCV related liver cirrhosis without HCC, group III had 25 healthy subjects as controls.

In this study, the serum levels of GP73 were highest in patients of group I with HCC compared to those with liver cirrhosis and the control groups.Also GP73 values increased with tumor number ,over all size and also correlated with vascular invasion, where as those of AFP correlated with vascular invasion and didn’t correlate with tumor number or size.

At a cut off value 5 , the diagnostic sensitivity and specificity of GP73 for selective detection of HCC over the cirrhotic group was 88% and 84.6% respectively.At a cut off value 7.12 , the diagnostic sensitivity and specificity of AFP for selective detection of HCC over the cirrhotic group was 76% and 76% .In conclusion, Golgi protein 73 can be used as a biomarker for hepatocellular carcinoma with a good diagnostic and prognostic value.

Key words: hepatocellular carcinoma, Golgi protein 73, alfa-feto protein

Contents

List of Abbreviations

AASLD	:	American Association for the Study of Liver Diseases
AFP	:	Alfa -feto protein
AFP-L3	:	Lens culinarisagglutinin-reactive alpha-fetoprotein
AFU	:	Alpha L-Fucosidase
AIDS	:	Acquired immunodeficiency syndrome
AJCC	:	American Joint Committee on Cancer
ALD	:	Alcoholic liver disease
ALP	:	Alkaline phosphatase
ALT	:	Alanine transaminase
AST	:	Aspartate transaminase
BCLC	:	Barcelona Clinic Liver Cancer
BMI	:	Body mass index
BUN	:	Blood urea nitrogen
CA	:	Cancer antigen
CD	:	Cluster of diffrentiation
CEA	:	Carcinoembyonic antigen
CK	:	Creatine kinase
CLIP	:	Cancer of the Liver Italian Program
Cr	:	Creatinine
CT	:	Computed tomography
DgCP	:	Des-gamma-carboxyprothrombin
DNA	:	Deoxyribonucleic acid
EASL	:	European Association for the Study of the Liver
ECM	:	Extracellular matrix
ECOG	:	Eastern Cooperative Oncology Group
EGF	:	Epidermal growth factor
EMT	:	Epithelial-mesenchymal transition
EPO	:	Erythropoietin
ETOH	:	Ethanol
GGT	:	Gamma-glutamyltranspeptidase

List of Abbreviations (Cont.)

GOLM1	:	Golgi membrane protein 1
GOLPH2	:	Golgi phosphoprotein 2
GP73	:	Golgi protein-73
GPC3	:	Glypican-3
Hb	:	Haemoglobin
HBeAg	:	Hepatitis B e antigen
HBsAg	:	Hepatitis B surface antigen
HBV	:	Hepatitis B virus
HCC	:	Hepatocellular carcinoma
HCV	:	Hepatitis C virus
HDV	:	Hepatitis delta virus
HIV	:	Human immunodeficiency virus
HLA	:	Human leukocyte antigen
HNE	:	Hydroxynonenal
HS-AFP	:	Hepatoma specific alfafeto protein
HSP	:	Heat shock protein
HTERT	:	Human telomerase reverse transcriptase mRNA
ICAM-1	:	Intercellular Adhesion Molecule 1
ICC	:	Intra hepatic cholangiocarcinoma
IGF-II	:	Insulin-like growth factor-II
IgG	:	Immunoglobulin G
IgM	:	Immunoglobulin M
IL 8	:	Interleukin-8
IL28B	:	interleukin-28B
INR	:	International normalized ratio
MAGE-1	:	Melanoma antigen gene
MELD	:	Model for end-stage liver disease
MMP	:	Matrix metalloproteinase
MRI	:	Magnetic resonance imaging
mRNA	:	Messenger RNA
MT1-MMP	:	Membrane-type matrix metalloproteinase 1
MWA	:	Microwave ablation

List of Abbreviations (Cont.)

NAFLD	:	Non-alcholic fatty liver disease
NASH	:	Non-alcholic steatohepatitis
NPV	:	Negative predictive value
5`-NPD	:	5`-Nucleotide phosphodiesterase
OLT	:	Orthotopic liver transplantation
OS	:	Overall survival
8-OHdG	:	8-hydroxydeoxyguanosine
PBC	:	Primary biliary cirrhosis
PDGF	:	Platelet derived growth factor
PEI	:	Percutaneous ethanol injection
PET	:	Positron emission tomography
PLT	:	Platelet
PPV	:	Positive predictive value
PSA	:	Prostatic specific antigen
PSC	:	Primary sclerosing cholangitis
PVE	:	Portal vein embolization
PVT	:	Portal vein thrombosis
RFA	:	Radiofrequency ablation
RNA	:	Ribonucleic acid
ROC	:	Receiver operating curve
SBP	:	Spontaneous bacterial peritonitis
SCCA	:	Serum squamous cell carcinoma antigen
SD	:	Standard deviation
SHARP	:	Sorafenib HCC Assessment Randomised Protocol
SPDI	:	Secreted protein discovery initiative
SU	:	Sunitinib malate
TACE	:	Transcatheter arterial chemoembolization.
TGF	:	Transforming growth factor
TGF-B1	:	Transforming growth factor-beta 1
TGF-β1	:	Transforming growth factor beta 1
TIMPs	:	Tissue inhibitors of metalloproteinases
TK	:	Tyrosine kinases
TMD	:	Transmembrane domain

List of Abbreviations (Cont.)

TNM	:	Tumor, Node, Metastasis
UICC	:	Union Internationale Contre le Cancer
UNOS	:	United Network for Organ Sharing
US	:	Ultrasound
VEGF	:	Vascular endothelial growth factor
WBC	:	White blood cell

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Introduction

Hepatocellular carcinoma (HCC) is a global health problem, although developing countries are disproportionally affected: over 80% of HCCs occur in such regions. Hepatocellular carcinoma (HCC) is strongly associated with either chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and is considered the fifth most common cancer and the third leading cause of cancer death worldwide ***(Shariff MI,2009).***

There were estimated 748,000 new cases of liver cancer worldwide in 2008, causing 696,000 deaths. Early detection of HCC is therefore extremely important in improving the survival of patients ***(Ferlay J et al.,2008).***

Alpha-fetoprotein (AFP) has been the only standard serum marker for the detection of HCC for the last 40 years, even though its sensitivity of 39-65% is not very satisfactory , so identification of better early diagnostic biomarkers is crucial ***(Shariff MI,2009).***

Studies have identified Golgi protein 73 (GP73; also named Golgi phosphoprotein 2(GOLPH2)), as a potential novel HCC serum marker GP73 is a 400 amino acid, 73 kDa trans membrane glycoprotein that normally resides within the cis-Golgi complex ***(Marrero JA et al,2005).***

Subsequent studies showed that the GP73 serum level is elevated in diverse viral and non-viral liver diseases, including hepatitis, cirrhosis and HCC, and also in non-liver malignances ***(Tan LY et al,2009)***.

Of significance is that serum GP73 is dramatically elevated in patients with HCC, and the sensitivity and specificity of GP73 for HCC might be superior to those of AFP ***(Hu JS,2010).***

Aim of the Work

The aim of this study is to determine the value of serum golgi protein 73 (GP 73) as a biomarker for HCC versus AFP in patients with HCV related liver cirrhosis.