The Diagnostic Value of Serum Interlukin-6 Versus Alpha Fetoprotein As A Tumor Marker for Hepatocellular Carcinoma In Egyptian Patients

Thesis

Submitted for the partial fulfillment of the master degree in
Internal Medicine

Presented by
Shady Samir Abdel Hamid Ghait
M.B.B.Ch., Ain Shams University (2011)

Under supervision of

Prof. Dr. Amal Shawky Mohamed Bakir

Professor of Internal Medicine, Gastroenterology and Hepatology
Faculty of Medicine - Ain Shams University

Dr. Ossama Ashraf Ahmed

Assistant Professor of Internal Medicine, Gastroenterology and Hepatology
Faculty of Medicine - Ain Shams University

Dr. Hany Haron Kaiser

Assistant Professor of Internal Medicine, Gastroenterology and Hepatology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2015

Acknowledgement

First, I would like to thank ***Allah*** *a lot for Blessing this work until it has reached its end, as a part of his generous help throughout our life.*

My profound thanks and deep appreciation to ***Prof. Dr. Amaal Shawky,*** *Professor of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University, for her great support and advice, his valuable remarks that gave me the confidence and encouragement to fulfill this work.*

I am also thankful to ***Dr. Osama Ashraf,*** *Assistant professor of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University, for his valuable supervision, co-operation and direction that extended throughout this work.*

I would like to direct my special thanks to ***Dr.Hany Haron,*** *Assistant professor of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University, for her invaluable help, fruitful advice, continuous support offered to me and guidance step by step till this thesis finished.*

My deep thanks to the subjects accepting participation in the study.

Finally my deep thanks to my colleagues and my family who supported me throughout my life.

Shady Ghait

List of Contents

List of Abbreviations

AAT	:	Alpha one anti-trypsin
AFP	:	Alpha-feto protein
AGP	:	Alpha one acid glycoprotein
AJCC	:	American Joint Committee On Cancer
ALP	:	Alkaline phosphatase
APC	:	Adenomatous polyposis coli
BCLC	:	Barcelona Clinic Liver Cancer
Bil	:	Billirubin
BMP	:	Bone morphogenic protein
CLIP	:	Cancer of Liver Italian Program
CT	:	Computed tomography.
DCP	:	Desgamma carboxy prothrombin
DKK1	:	Dickkopf 1
ECOG	:	Eastern cooperative oncology group
EGF	:	Epidermal growth factor
EGFR	:	Epidermal growth factor receptor
EpCAM	:	Epithelial cell adhesion molecule
ERK	:	Extracellular signal-regulated kinase
EUS	:	Endoscopic ultra sonography
FGF	:	Fibroblast growth factor
FLK-1	:	Fetal liver kinase
FLT-1	:	Fms-like tyrosine kinase
GDP	:	Guanosine 5'-diphosphate
GGT	:	Gamma-glutamyl transpeptidase
GLYP3	:	Glypican-3
GP73	:	Golgi protein 73
HCC	:	Hepatocellular carcinoma
HIFU	:	High intensity focus ultrasound
HSP70	:	Heat shock protein 70
IGF	:	Insulin like growth factor
IL-1	:	Interlukin-1
IL-6	:	Interlukin-6

List of Abbreviations (Cont.)

IR	:	Insulin receptor
JIS	:	Japan Integrated Staging score
K19	:	Keratin 19
LFT	:	Liver function tests
MELD	:	Model for endstage liver disease
miR	:	Micro RNA
MRI	:	Magnetic resonance imaging.
m-RNA	:	Messenger RNA
MSCT	:	Multi-Slice CT
NAFLD	:	Nonalcoholic fatty liver disease
NASH	:	Nonalcoholic steatohepatitis
NK cells	:	Natural killer cells
OPN	:	Osteopontin
PEI	:	Percutaneous ethanol injection
PIVKA II	:	Prothrombin induced by Vitamin K Absence II
PLGF	:	Placental growth factor
PT	:	Prothrombin time
PVT	:	Portal vein thrombosis
RCT	:	Randomized control trial
RFA	:	Radiofrequency ablation
TACE	:	Transarterial chemoembolization
TE	:	Transient elastography
TGF	:	Transforming growth factor
US	:	Ultrasonography
VEGF	:	Vascular endothelial growth factor
VEGFR	:	Vascular Endothelial Growth Factor Receptors

List of tables

List of tables (Cont.)

List of Figures

List of Figures (Cont.)

Introduction

Hepatocellular carcinoma (HCC) is an increasingly prevalent clinical problem worldwide and is the fifth most common cause of cancer-related death, results in between 250, 000 and one million deaths globally per annum. HCC has unique geographic, sex, and age distributions that are likely determined by specific etiologic factors (**Venook et al., 2010)**

Cirrhosis of any etiology is the most common risk factor for HCC development. Over 90% of HCCs develop on a cirrhotic liver resulting from either chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, alcohol abuse, or accumulation of fat referred as nonalcoholic steatohepatitis (**Sanyal, Yoon& Lencioni, 2010)**.

Hepatocellular carcinoma (**HCC**) is one of the three most frequently diagnosed cancers in Egypt (**Gomaa et al., 2008**). HCC is the fifth most common malignancy in the world and the third most common cause of cancer-related death (**Ahmedin et al., 2008**).

The major risk factors for the development of HCC were liver cirrhosis, viral hepatitis (chronic hepatitis B and hepatitis C), toxic (alcohol and aflatoxins), metabolic (Diabetes with non-alcoholic fatty liver disease, hereditary haemochromatosis) and immune-related (primary biliary cirrhosis and autoimmune hepatitis) (**Parikh and Hyman, 2007**).

Peng et al. (2009) reported that for HCC, surgical resection can be offered to patients with a solitary lesion if they are non-cirrhotic, or have cirrhosis but still have well-preserved liver function. Liver transplantation is an effective option for patients with a solitary lesion <5 cm or up to 3

lesions, each <3 cm in diameter. Percutaneous radiofrequency ablation (PRFA) has emerged as a excellent treatment modality because of its effectiveness and safety for small HCC (<5.0 cm).

Most HCCs are diagnosed at an intermediate to advanced stage, and few meaningful therapeutic options are available at this point **(Stefaniuk et al., 2010)**. Transcatheter arterial chemoembolization (TACE) is currently considered as a primary and complementary measure for the treatment of unresectable hepatocellular carcinoma and metastatic liver cancer (**Cazejust et al., 2010**).

The tests used to diagnose HCC include radiology, biopsy and Alfa Fetoprotien (AFP) serology (**Forner et al., 2008**). AFP has been used as a serum marker for HCC for many years. AFP seems to be of prognostic value at the time of tumor diagnosis. A high AFP concentration (≥ 400 ng/mL) in HCC patients is associated with greater tumour size, bilobar involvement, portal vein invasion, and a lower median survival rate (**Grizzi et al., 2007**). But AFP plays alimited role in detection and diagnosis of HCC. Some new candidate biomarkers for the diagnosis of HCC have been investigated (**Hui et al., 2010**).

Aim of the Work

The aim of this work is to evaluate the diagnostic value of interleukin-6 in comparison to alphafetoprotein as a tumour marker for hepatocellular carcinoma in Egyptian patients.

Chapter (1):

Hepatocellular Carcinoma

Epidemiology:

Hepatocellular carcinoma (HCC) is the most common tumor worldwide and the leading cause of death amongest patients with cirrhosis. More than 600 000 deaths globally per year have been reported, with 82% of cases occurring in "developing" countries **(Khalid and Bouneva et al., 2011).**

High incidence regions (more than 15 cases per 100,000 populations per year) include sub-Saharan Africa, China, Hong Kong and Taiwan. The incidence is 24.2/100,000 in parts of Africa and the 35.5/100,000 seen in eastern Asia. Japan has one of the highest incidence rates of HCC associated with chronic HBV infection. The incidence tends to be decreasing yearly **(Yang et al., 2010).**

In Egypt, epidemiology of HCC is characterized by marked demographic and geographic variations. Over the last decade, a remarkable increase, from 4.0% to 7.2%, was observed in the proportion of chronic liver disease (CLD) patients with HCC. The predominant age group (40-59 years) showed a slight increase compared with older groups (> 60 years). A significant increase, from 82.5% to 87.6%, was observed in the proportion of HCC among males. The calculated risk of HCC development is nearly three times higher in men than in women. A unique invisible risk factor for development of HCC in Egypt could be Schistosomal infection. Schistosomiasis induces immune suppression, which could result in increased persistence of viremia following acute infection of both hepatitis B and C **(Abd Elhamid et al., 2011).**

Risk factors:

Approximately 70% to 90% of patients with HCC have an established background of chronic liver disease and cirrhosis, with major risk factors for developing cirrhosis including chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), nonalcoholic steatohepatitis (NASH) alcoholic liver disease, diabetes, obesity, hereditary liver disease as Wilson's disease hereditary haemo-chromatosis, iron overload syndromes, alpha 1 antitrypsin deficiency and hereditary tyrosinemia, autoimmune Liver diseases as autoimmune hepatitis and primary biliray cirrhosis, aflatoxin, alcohol intake, smoking & tobacco, gender, hepatic adenoma and family history **(Poon, 2009).**

Liver Cirrhosis

The prevalence of cirrhosis in patients with HCC is about 80% to 90% in autopsied series worldwide and therefore, approximately 10% to 20% of cases of HCC develop in persons without cirrhosis **(Schlansky et al., 2011).**

Among HCC cases with cirrhosis, HCV infection was identified in 27% to 73%, HBV infection in 12% to 55%, heavy alcohol intake in 4% to 38%, and hemochromatosis and other causes in 2% to 6% leaving 4% to 6% of the total number of cases without an identified cause. On the other hand persons with HCC without underlying cirrhosis, HCV infection accounted for 3% to 54%, HBV infection for 4% to 29%, heavy alcohol intake for 0% to 28% and less common conditions for 1% to 5% of the cases. In a variable proportion of HCC cases, the etiology was unknown **(Montella et al., 2011)**.