Assessment of Serum Matrix MetalloProteinase 2 (MMP-2) in Patients with Liver Cirrhosis and Hepatocellular Carcinoma and its Clinical Significance

Thesis

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بسم الله الرحمن الرحيم

"قالوا سبحانكَ لا عِلمَ لنا إلاّ ما
علّمتنا إنّكَ أنتَ العَليمُ
الحكيمُ"

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LIST OF ABBREVIATIONS

A_1AT = Alpha 1- Antitrypsin

AASLD = American Association for the study of liver diseases

Abs = Antibodies

ADAM-9 = A Disintegrin And Metalloprotease-9

AFB1 = Aflatoxin-B1

AFP = Alpha-Feto Protein

AJCC = American Joint Committee on Cancer

ALP = Alkaline Phosphatase

ALT = Alanine Transaminase

ANA = Anti-Nuclear Antibody

APC = Antigen-presenting cells

ASMA = Anti-smooth muscle antibody

AST = Aspartate transaminase

BCLC = Barcelona Clinic Liver Cancer

CBC = Complete blood count

CCl_4 = Carbon tetrachloride

CLIP = Cancer of the Liver Italian Parogram

CT = Computed tomography

CTAP = Arterioportal CT

CTP = Child-Turcotte-Pugh

CUPI = Chinese University Prognostic Index

DEXA = Dual x-ray absorptiometry

DNA = DeoxyriboNucleic Acid

EASL = European association for the study of the liver

ECM = Extracellular matrix

EMT = Epithelial-mesenchymal transition

FNA = Fine Needle Aspiration

GIT = Gastrointestinal tract

HBeAb = Hepatitis B e antibody

HBV = Hepatitis B virus

HCC = Hepatocellular carcinoma

HCV = Hepatitis C virus

HRS = Hepato-renal syndrome

HSC = Hepatic stellate cell

IFN = Interferon

IGF-1 = Insulin-like growth factor 1

INR = International Normalized Ratio

IPF = Interstitial lung fibrosis

IV = Intravenously

LDH = Lactate dehydrogenase

LDLT = Living donor liver transplantation

LT = Liver transplantation

MFB = Myofibroblast

MMPs = Matrix metalloproteinases

MRI = Magnetic resonance imaging

MT_1-MMP = Membrane type 1-MMP

NAFLD = Non-Alcoholic Fatty Liver Disease

NASH = Non-Alcoholic SteatoHepatitis

PBC = Primary biliary cirrhosis

Pc = Prothrombin concentration

PDGF = Platelet-derived growth factor

PMNL = Polymorphonuclear leukocyte

PT = Prothrombin Time

RBC = Red blood cell

RCTs = Randomized cohort trials

RECIST = Response Evaluation Criteria in Solid Tumours

SAAG = Serum-ascites albumin gradient

SBP = Spontaneous bacterial peritonitis

SPECT = Single-photon emission tomography, or positron CT

TGFβ1 = Transforming growth factor beta-1

TIMPs = Tissue inhibitors of metalloproteinases

TIPS = Transjugular intrahepatic portosystemic shunt

TIPS = Transjugular intrahepatic portosystemic shunt

TP = Total protein

WBC = White blood cell

WHO = World Health Organization

INTRODUCTION:

Liver fibrosis and its end-stage sequelae cirrhosis represent a major worldwide health problem **(Bedossa et al., 2003).** Cirrhosis is defined histologically as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. Cirrhosis of the liver is the end stage of a complex process resulting from hepatocyte injury and the response of the liver that leads to partial regeneration and fibrosis. The progression of liver injury to cirrhosis may occur over weeks to years **(Bravo et al, 2001).**

Chronic liver disease and cirrhosis result in about 35,000 deaths each year in the United States. Cirrhosis is the ninth leading cause of death in the United States and is responsible for 1.2% of all US deaths. Many patients die from the disease in their fifth or sixth decade of life **(Butler et al, 2004).**

Hepatocellular carcinoma (HCC) is a primary malignancy of the hepatocyte, generally leading to death within 6-20 months. HCC frequently arises in the setting of cirrhosis, appearing 20-30 years following the initial insult to the liver. However, 25% of patients have no history or risk factors for the development of cirrhosis **(Llovet et al, 2003).**

Estimates from the year 2000 indicate that liver cancer remains the fifth most common malignancy in men and the eighth in women worldwide. The number of new cases is estimated to be 564,000 per year, including 398,000 in men and 166,000 in women. Rates of liver cancer in men are typically 2

to 4 times higher than in women. The incidence of primary liver cancer is increasing in several developed countries, and the increase will likely continue for some decades **(Bosch et al, 2004).**

Advanced and metastatic HCC remain challenging diseases to treat, furthermore the underlying cirrhotic condition of the liver that in most instances accompanies HCC provides an additional treatment challenge **(Ghassan Abou-Alfa 2006).**

Liver fibrosis is thought to be a progressive pathological process that leads ultimately to deposition of excess matrix proteins in extracellular space, and destroys normal liver architecture to finally result in cirrhosis **(Benyon RC et al, 2001).** Liver fibrosis occurs as a consequence of net accumulation of matrix proteins (especially types I and III collagen) in response to liver injury. Liver fibrosis is underpinned by the activation of hepatic stellate cells (HSCs) to a myofibroblast like phenotype with a consequent increase in their synthesis of matrix proteins such as interstitial collagens that characterize fibrosis **(Guang-Fu Xu et al, 2004).**

This activated phenotype of HSCs subsequently becomes the major source of the interstitial collagens. It has been suggested that HSCs are also a source of matrix-degrading metalloproteinases (MMPs), indicating their participation in matrix remodeling. As a family of neutral proteinases, MMPs act on a variety of substrates. Different expression profiles of MMPs influence the outcome of extracellular matrix components, resulting in preferential accumulation of interstitial collagens **(Benyon et al, 2001) & (Okazaki et al, 2000).**

In extracellular space, matrix degradation occurs predominantly consequent to the action of a family of enzymes known as matrix metalloproteinases (MMPs), **(Benyon et al, 2001).** By definition progressive fibrosis occurs when the rate of matrix synthesis exceeds matrix degradation **(Bedossa et al, 2003).**

These Gelatinases (MMP -2 and MMP-9) have an important role in the pathogenesis of liver cirrhosis (LC) and hepatocellular carcinoma (HCC) **(Kwon et al, 2003).**

The balance between activated MMPs and their free inhibitors determines the net MMP activity and seems to be of great importance for matrix protein turnover associated with tumor cell invasion and metastasis. A striking phenotypic characteristic of fibrotic liver is a dramatic up-regulation of TIMP-1 which is one of the tissue inhibitors of MMPs, and at the same time seems to be a functional promotor of hepatic fibrosis. **(Mc Crudden et al, 2000).**