Transforming Growth Factor-beta 1 and Follistatin in Patients with Hepatocellular Carcinoma and Patients with Liver Cirrhosis

Thesis

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List of Abbreviations

Abbrev.	
AFB1	Aflatoxin B1
AFU	Alpha-l-fucosidase
Ang-1	Angiopoitin-1
Ang-2	Angiopoitin-2
Bcl-2	B-cell lymphoma 2
BCLC	Barcelona Clinic Liver Cancer
Bcl-xl	Bcl–associated X protein
BFGF	Basic fibroblast growth factor
CD	Cluster of differentiation
CgA	Chromogranin A
CGH	Comparative genomic hybridization
CK	Cytokeratin
DCP	des gamma carboxy prothrombin
DFS	Disease-free survival
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptors
ELISA	Enzyme linked immunosorbant assay
FGF	Fibroblast growth factor
FST	Follistatin
GEP	Granulin-epithelin precursor
GGT mRNA	Gamma-glutamyl transferase mRNA
GP73	Golgi Protein 73

List of Abbreviations (Cont.)

Abbrev.	
GPC3	Glypican-3
HALT-C	Hepatitis c long term treatment against cirrhosis
HBsAg	HBV surface antigen
HBV	Hepatitis c virus
HCC	Hepatocellular carcinoma
HCCR	Human Cervical Cancer Oncogene
HCV	Hepatitis c virus
HGDN	High-grade dyspastic nodules
HSAFP	Hepatoma-specific AFP
HSP	Heat shock protein
HSP	Heat shock protein
ICC	Intrahepatic cholangiocarcinoma
IGF-II	Insulin-like-growth factor II
IL-8	Interleukin-8
LCA	Lens culinaris agglutinin
LIs	Labeling indices
LOH	Loss of heterozygosity
MDCT	Multidetector CT scan
MELD	Score model for end stage liver disease
MMPs	Matrix metalloproteinases
MRI	Magnetic resonance imaging

List of Abbreviations (Cont.)

Abbrev.	
NAFLD	Non alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCI	National Cancer Institute
NF kappa B	Nuclear factor kappa-light-chain-enhancer of activated B cells
PBMCs	Peripheral blood mononuclear cells
PDGFR	Platelet-derived growth factor receptor
PIVKA II	Prothrombin Induced by Vitamin K Absence II
RCTs	Randomized controlled trials
RECIST	Response Evaluation Criteria In Solid Tumours VEGFR-2 vascular endothelial growth factor receptor
RFA	Radio frequency ablation
ROC curve	Receiver operator characteristic curve
RT-PCR	Reverse transcriptase polymerase chain reaction
SEER	Epidemiology and End Results
SPSS	Statistical program for social science
TAA	Tumor-Derived Autoantibody
TACE	Trans arterial chemo embolization
TAE	Transcatheter arterial embolization
TGF-β1	Transforming growth factor beta 1
TIMPs	Matrix metalloproteinase inhibitors

List of Abbreviations (Cont.)

Abbrev.

TNM ..... Classification tumor, nodes, metastasis

TSGF..... Tumor-specifi c growth factor

TTP ..... Time to progression

UNOS ..... United Network for Organ Sharing

VEGF ..... Vascular endothelial growth factor

WHO..... World health organization

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First of all, thanks to ***Allah*** *for helping and guiding me in accomplishing this work and for everything else I have.*

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the predominant form of primary malignancy of the Liver and rapidly reduces quality of life and typically causes death 6 months−1 year from diagnosis ***(Bosch et al., 2005).***

Globally, it is the fifth leading cause of cancer and the third leading cause of cancer death ***(Yu et al., 2000).***

This cancer varies widely in incidence throughout the world, with rising incidence in Egypt ***(Bosch et al., 2005).***

Hospital-based studies from Egypt have reported an overall increase in the relative frequency of all liver-related cancers in Egypt (>95% as HCC), from approximately 4% in 1993 to 7.3% in 2003 ***(El-Zayadi et al., 2005)***

The primary risk factors for hepatocellular carcinoma (HCC) are hepatitis B virus (HBV), hepatitis C virus (HCV), dietary aflatoxin exposure, and chronic alcohol consumption ***(El-Serag et al., 2007).***

Diagnosis is often occurs late and prognosis for HCC remains poor and despite recent advances, the molecular pathology of the disease is not well understood and the therapeutic possibilities are largely limited to either surgical procedures or liver transplantation, or local tumor ablation ***(Deli et al., 2008)***

Serum α-fetoprotein, the currently used clinical marker, is elevated in only 60% of HCC patients, therefore the identification of additional markers is expected to have significant public health impact ***(Goldman et al, 2009).***

Deregulated expression of growth factors and their cognate receptors has been described in hepatocellular carcinoma for both, positive regulators of hepatocyte growth, such as insulin-like growth factor 2 (IGF-2), hepatocyte growth factor (HGF), and transforming growth factor α (TGF α),as well as for negative regulators like TGFβ ***(Breuhahn et al., 2006).***

Transforming growth factor- beta (TGFβ1) exerts an inhibitory effect on DNA synthesis of hepatocytes, follistatin antagonize the actions of activin which exhibits an apoptotic effect on hepatocytes through different mechanism other than TGFβ1 ***(Deli et al., 2008).***

AIM OF THE WORK

To investigate the role of TGFβ1 and follistatin in the diagnosis of HCC.

HEPATOCELLULAR CARCINOMA

Introduction

Hepatocellular carcinoma (HCC) is one of the deadliest forms of cancer worldwide, with a5-year survival rate of less than 5%. The high death rate is due in part to the fact that liver cancer is often detected at advanced stages. This is particularly problematic because, apart from surgical resection or ablation of the primary tumors, no curative treatment options are available ***(Poon et al., 2009).***

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third leading cause of cancer mortality worldwide ***(Wang, 2010).***

HCC is characterised by rapid tumour growth and a high propensity of vascular invasion. Furthermore, 80% of patients with HCC have associated liver cirrhosis related to hepatitis B or C viral infection, which often restricts treatment options because of impaired liver function. The prognosis of untreated HCC is poor, but the management approach of HCC has changed from a previously nihilistic approach to a more aggressive one with recent advances in management, resulting in improved prognosis. The wider utilisation of screening programme in high-risk patients has resulted in early detection of small HCCs, and thus improved chance of treatment ***(Poon, 2010).***