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Faculty of Medicine

STUDY OF TREATMENT AND ANTIANGIOGENESIS OF HEPATOCELLULAR CARCINOMA

Essay

Submitted for partial fulfillment of Master degree in Internal Medicine

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2011

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿ قَالُوا سُبْحَنَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا

﴿ إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ ﴾

صدق الله العظيم

(البقرة ٣٢)

Acknowledgement

*First and foremost thanks to Allah the most merciful. I would like to express my deep sincere gratitude to **Prof. Dr. Mohamed Aly Maraey Makhoul** Prof. of Internal Medicine, Faculty of Medicine, Ain Shams University, for his fatherly attitude, kind supervision, continuous encouragement and valuable advice.*

*Cordial thanks are owed to **Prof. Dr. Essam Farid Mahdy** Professor of Internal Medicine, Faculty of Medicine, Ain Shams University, for his unlimited help during this work.*

*Sincere gratitude and deepest thanks are owed to **Dr. Maha Mohsen Kamal ElDin** Lecturer of Internal Medicine, Faculty of Medicine, Ain Shams University, for her valuable assistance, kind advice and continuous encouragement.*

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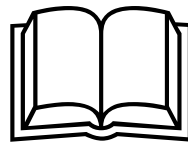
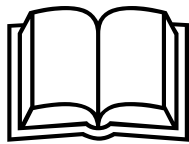
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List of Abbreviations

<i>Abbreviation</i>	<i>Title</i>
a FGF	Acidic fibroblast growth factor.
AF	Aflatoxin.
AFP	Alpha feto protein
AFU	Alpha 1- flucosidase.
AASLD	American Association for the Study of Liver Disease.
AJCC	American Joint Committee on Cancer
Ang pl3	Angiopoietin like 3
BCLC	Barcelona Clinical Liver Cancer.
bFGF	basic fibroblast growth factor.
bm-JIS	Biomaker –combined Japanese integrated scoring system.
B	Bevacizumab.
CLT	Cadaveric liver transplantation.
CLIP	Cancer of the Liver Italian Program.
CP	Child Pugh
CUPI	China University Prognostic Index.
CLD	Chronic liver disease.
CT	Computerised tomography.
CECT	Contrased enhanced helical computerized tomography.
CEUS	Contrast enhanced ultrasound.
DCP	Des gamma carboxyprothrombin.
DEB	Doxorubicin-eluding beads.
ECOG	Eastern Cooperative Oncology Group.
ECM	Endothelial cell membrane.
EC	Endothelial cell.
EGFR	Epidermal growth factor receptor.
E	Erlotinib.
EASL	European Association for the Study of Liver Disease.
FDA	Food and Drug Administration.
FNAC	Fine needle aspiration cytology.
GPC3	Glypican 3.
HBV	Hepatitis B virus.
HCV	Hepatitis C virus.
HSCs	Hepatic stellate cells.
HCC	Hepatocellular carcinoma.
HGF	Hepatocyte growth factor.
HIF-1alpha	Hypoxia inducible factor-1 alpha

<i>Abbreviation</i>	<i>Title</i>
HREs	Hypoxia responsive elements.
HIV	Human immunodeficiency virus.
IC	Immuocomplexes.
IGF-2	Insulin growth factor 2.
IL2	Interleukin2.
INR	International normalization ratio.
JIS	Japanese Integrated Score.
LSECs	Liver sinusoidal endothelial cells.
LT	Liver Transplantation.
LDLT	Living donor liver transplantation.
MRI	Magnetic resonance imaging.
MNL	Maximum normal limit.
MWA	Microwave ablation .
MDCT	Multi detector helical computerized tomography.
MPCT	Multi phasic helical computerized tomography.
NO	Nitric oxide .
NAFLD	Non- alcoholic fatty liver disease.
NASH	Non-alcoholic steato-hepatitis.
OLT	Orthotopic liver transplantation.
OS	Overall survival.
PAT	Parenteral anti schistosomal therapy.
PR	Partial response .
PEI	Percutaneous ethanol injection.
PST	Performance status test.
PDGFR	Platelat derived growth factor receptor.
PD	Progressive disease.
PFS	Progression free survival.
RFA	Radiofrequency ablation.
Raf /MEK/ERK	Raf /mitigen activated protein kinase/extracellular signal regulated kinase.
RCTs	Randomised controlled trials.
RECIST	Response evaluation criteria in solid tumors.
RNA	Ribonucleic acid.
Sf	Sorafenib.
SHARP	Sorafenib HCC Assesement Randomised Protocol.
SCCA	Squamous cell carcinoma antigen.
SD	Stable disease.
TTP	Time to time progression.
TGF	Transforming growth factor.
TGFbeta1	Transforming growth factor beta 1.

<i>Abbreviation</i>	<i>Title</i>
TACE	Transarterial chemoembolisation.
Tx	Treatment.
TNF	Tumor necrosis factor.
TNM	Tumor –Node –Metastasis.
UNOS	United Network for organ sharing.
UCSF	University of California San Francisco.
US	Ultrasonography.
ULN	Upper limit of normal.
VE-Cadh	Vascular endothelial cadheren.
VEGF	Vascular endothelial growth factor.
VEGFR	Vascular endothelial growth factor receptor.
VE-PTP	Vascular endothelial phosphatase.
WHO	World health organization.
Y90	Yttrium-90



Introduction and Aim of the Work

INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary malignancy of liver cells. It is the fifth most common cancer in the world accounting for an estimated half million deaths annually (*Zhu et al., 2008*).

Therapies for HCC have remarkably developed during the last decades and prognosis of HCC patients has subsequently much improved (*Seki et al., 2007*).

Surgical resection remains the treatment of choice for patients with a single lesion and well preserved liver function with a 5 year survival rates of at least 50-70% (*Kothary et al., 2007*).

Non- Surgical treatment include : Ablative therapy (*Ryder, 2003*), Trasarterial Chemoembolisation (*Jelic , 2009*), Yttrium-90 labelled Microspheres (*Sangro et al., 2009*) and Chemotherapy (*Abou-Alfa , 2007*).

Liver transplantation is considered the only curative treatment . It offers the benefit of eradicating the tumor and treating the underlying disease (*Ryder, 2003*).

Antiangiogenic therapy for HCC:

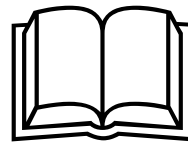
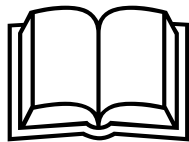
HCC is a highly vascular tumor and requires angiogenesis to grow beyond a few millimeters in size. Angiogenesis is evident in early stage liver carcinoma and correlates with disease progression. The primary stimulus for tumor angiogenesis is vascular endothelial growth factor (VEGF), an endogenous cytokine that induces capillary endothelial cell proliferation, migration and survival, and the induction of bone marrow derived endothelial progenitor cells (EPCs) to the new vasculature. Other angiogenic factors, such as platelet-derived growth

factor (PDGF) and basic fibroblast growth factor (bFGF), are also expressed in HCC (*Zhu et al., 2008*).

The inherent vascularity of HCC makes it a logical target for antiangiogenic therapy. **Sorafenib** (Nexavar) and **sunitinib** (Sutent) are orally administered small molecule tyrosine kinase inhibitors (TKIs) that bind competitively to the intracellular receptor domains for VEGF, PDGF, and other angiogenic growth factors. Based on positive phase 3 trial results, sorafenib is now approved for advanced, unresectable HCC in U.S and Europe. Phase 2 data of sunitinib in advanced HCC have recently been presented. **Bevacizumab** (Avastin), a humanized monoclonal antibody that binds circulating VEGF, is also in phase 2 trials for advanced HCC (*Abou -Alfa et al., 2007*).

AIM OF WORK

The aim of work is to review an essay of recent modalities of treatment of hepatocellular carcinoma including interventional and antiangiogenic medications.



Review of Literature
