Stem Cell Transplantation in Advanced Hepatocellular Carcinoma

Essay Submitted For Partial Fulfillment of Master Degree of Internal Medicine

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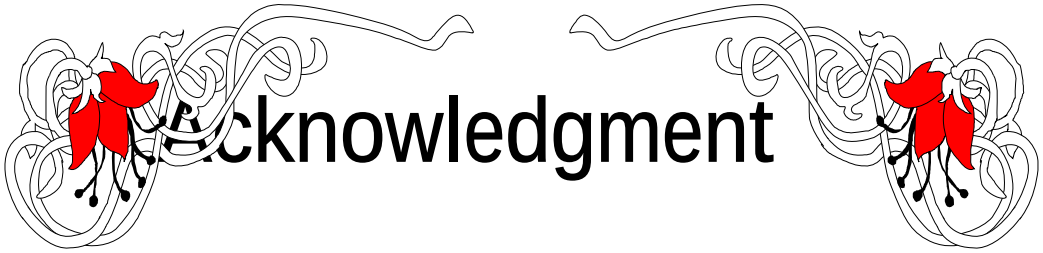
(بسم الله الرحمن الرحيم)

سَنُرِيهِمْ آيَاتِنَا فِي الأفَاقِ وَفِي أَنفُسِهِمْ حَتَّى يَتَبَيَّنَ لَهُمْ أَنَّهُ الْحَقُّ أَوَلَمْ يَكْفِ بِرَبِّكَ أَنَّهُ عَلَى كُلِّ شَيْءٍ شَهِيدٌ.

(صدق الله العظيم)

فُصِّلَتْ (53)



Thanks and Praise to God for helping us to make this piece of work come into light

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List of Abbreviations

AASLD: The American Association for the Study of the Liver Diseases.

ADASs: Adipose-derived adult stem cells.

ADSCs: Adipose-derived stromal cells.

AE cells: Amniotic epithelial cells.

AFB1: Aflatoxin B1.

AFP: α-fetoprotein.

ALF: Acute liver failure.

ALT: Alnine aminotransferase.

AR: androgen receptor

ASL: Argininosuccinate lyase.

ATSCs: Adipose tissue-derived stromal cells.

BCLC: Barcelona Clinic Liver Cancer.

bFGF: Basic fibroblast growth factor.

BM: Bone marrow.

BMHSCs: Bone marrow

cGMP :current Good Manufacturing Protocols .

CLIP score: Cancer of the Liver Italian Program score.

CLT: Cadaveric liver transplantation.

CP SCORE: Child-Pugh score.

CUPI: The Chinese University Prognostic Index.

EASL: The European Association for the Study of the Liver.

EGF: Epidermal Growth Factor.

ESC: Embryonic stem cell.

FAH: Fumarylacetate hydrolase.

FDA: Food and Drug Administration. .

FGF: Fibroblast growth factor.

G-CSF: Granulocytes colony stimulating factor.

GRETCH score: The Groupe d'Etude de Traitement du Carcinoma Hepatocellulaire score.

HBsAg: hepatitis B surface antigen.

HBV: Hepatitis B virus.

HCC : Hepatocellular carcinoma.

HCV: Hepatitis C virus.

HGDN: High grade dysplastic nodule.

HGF: Hepatocyte growth factor

HNF: Hepatocyte nuclear factor.

HOCs: Hepatic oval cells.

HPC: Hepatic progenitor cells.

HSCs: Hematopoietic stem cells.

IL-12: Interleukin 12.

INR: International normalised ratio.

JIS score: Japan Integrated Staging score.

KIT: v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog.

LDLT: Live-donor liver transplantation.

M1: Metastatic spread.

MAPCs: Multipotent adult progenitor cells.

MELD score: Model for end stage liver disease.

MSCs: Mesenchymal stem cells

N1: lymph node involvement.

OC.2: Oryctolagus cuniculus.

OLT: Orthotopic Liver Transplantation.

PCNA: Proliferating cell nuclear antigen.

PDSCs: Placenta-derived stem cells

PEDF: Pigment epithelium-derived factor.

PEI: Percutaneous ethanol injection.

PS: Performance status.

PVE: Portal venous embolization.

RF: Radiofrequency ablation.

RLV: Remnant liver volume.

SCF: Stem cell factor.

SPVE: Selective portal venous embolization

TACE: Transarterial chemoembolization.

TAE: Transarterial embolization.

Thy-1: Thymus cell antigen 1.

TLV: total liver volume.

UICC: Union International Contre Cancer.

US: Ultrasound.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common human cancer with a global incidence of 500.000 new cases per year and the third most frequent cause of cancer death worldwide with nearly 600.000 deaths each year , exceeded only by cancers of the lung and stomach *(El-Serag and Rudolph, 2007).*

The major risk factor for the development of HCC is cirrhosis of the liver. However, about one quarter of HCC cases diagnosed in the United States do not have any known predisposing risk factors. The major known risk factors for HCC are viral (chronic hepatitis B and hepatitis C), toxic (alcohol and aflatoxins), metabolic (diabetes, non-alcoholic fatty liver disease and hereditary haemochromatosis) and immune-related (primary biliary cirrhosis and autoimmune hepatitis) *(Gomaa et al., 2008).*

With the increased awareness of HCC, more asymptomatic patients are being diagnosed as part of active surveillance. Unfortunately, the majority of patients still presents with signs and symptoms suggestive of liver decomposition and/or tumor spread *(El–Serag et al., 2008).*

A majority of HCC patients present in advanced stage (with Eastern Cooperative Oncology Group [ECOG] 1–2 performance status or vascular invasion ⁄ extra-hepatic spread) and have a median survival of 6 months *(Chaparro et al., 2008).*

Current available therapeutic modalities for HCC are largely inadequate. Surgical approaches such as resection and transplantation are the treatment of choice for HCC; however, because of underlying liver disease, only a minority of patients is suitable for resection, and access to transplantation is limited by organ availability. Local tumor ablation is effective for early HCC, and chemoembolization is of benefit in intermediate-stage disease. So far, no first-line therapy has emerged for advanced HCC. For these patients, systemic therapy is indicated but has been largely unsuccessful. Therefore, there exists a clear demand for effective, life-prolonging therapeutic strategies for the large number of HCC patients with advanced disease (*Schwartz et al., 2007; Shen et al., 2008).*

The medical community is currently experiencing a wave of enthusiasm for the clinical trials, in which stem/progenitor cells are used for liver regeneration .this is based on promising results in animal models and encouraging reports from some initial clinical studies *(Herr et al., 2007).*The considerable excitement surrounding the possible use of stem cells for liver diseases is based on the peculiar features of these cells, able to self-renew, regenerate and transdifferentiate. Transplantation of autologous stem cells has long been used to treat patients with haematopoietic malignancies and, subsequently, to enhance stem-cell mobilization and left ventricule injury repair after myocardial infarction *(Gasbarrini et al., 2007).*

Evidence has been presented that not only hematopoietic stem cells, but also Bone Marrow derived Mesenchymal Stem Cells [BM-derived MSCs] can be expanded and differentiated into hepatocyte progenitor cells *(Alison and Lovell 2005).*

Hepatocyte transplantation has been performed for a variety of indications, including acute liver failure, end stage liver disease (ESLD), and inborn errors of metabolism *(Fisher and Strom, 2006).*

Am Esch et al. in 2005 suggested that the novel therapeutic approach using the application of CD133+ cells to the portal vein may bear the potential for augmentation of liver regeneration before extensive hepatectomy in a clinical setting.

In patients with malignant liver lesions, in particular patients with very small left lateral segments, a large and fast-progressing tumor mass, and limited quality of hepatic parenchyma, CD133+ stem cells may be a powerful adjunct to Portal Vein Embolization [PVE]. The combination of PVE with CD133+ BMSC administration substantially increased hepatic regeneration compared with PVE alone *(Fürst et al., 2007).*

Due to the poor proliferative capacity of liver cells in end-stage liver diseases, stem cell may play an important role in liver regeneration and may be a therapeutic option for HCC *(Sun and Zuo, 2008).*

AIM OF THE WORK

To make comprehensive review of literature on recent advances in stem cell therapy in the advanced hepatocellular carcinoma.

HEPATOCELLULAR CARCINOMA

Epidemiology:

Hepatocellular carcinoma (HCC) is a primary cancer of the liver that accounts for between 85% and 90% of primary liver cancers. HCC is the fifth most common human cancer with a global incidence of 500.000 new cases per year and it is the third most frequent cause of cancer death worldwide with nearly 600.000 deaths each year, exceeded only by cancers of the lung and the stomach *(El-Serag and Rudolph, 2007).*

The incidence ranges from 10 cases per 100,000 population per year in North America and Western Europe to 50–150 cases per 100,000 population per year in parts of Africa and Asia where HCC is responsible for a large proportion of cancer deaths *(Spangenberg et al ., 2008).*

The global age distribution of HCC varies by region, incidence rate, sex, and, possibly, by etiology *(Parkin, 2002).* The incidence of HCC increases with age, reaching its highest prevalence among those aged over 65 years *(Bosch et al., 2004;Parikh et al., 2007).*Although HCC is rare before the age of 50 years in North America and Western Europe, a shift in incidence towards younger persons has been noted in the last two decades *(Bosch et al., 2004)* .