EARLY DETECTION OF HEPATOCELLULAR CARCINOMA IN HEBATITIS "C" CIRRHOTIC PATIENTS

Thesis
Submitted for partial fulfillment of Master Degree
In Tropical Medicine

By

Rabab Abdel Salam Nashaát Moharram

M.B.B.Ch

Supervised by

Prof. Dr: Ashraf Omar Abdel-Aziz

Professor of Tropical Medicine
Faculty of Medicine, Cairo University

Prof. Dr: Abdel- Rahman Nabawi Zekri

Professor of Biology& Immunology in National Institute of Cancer
Cairo University

Dr: Hesham Ibrahim Al-Makhzangy

Lecturer in Tropical Medicine
Faculty of Medicine, Cairo University

Faculty of Medicine
Cairo University
2008

الكشف المبكر عن سرطان الكبد
في المرضي المصابين بتليف الكبد نتيجة الأصابة
بالألتهاب الكبدي المزمن "سى"

دراسة مقدمة من

الطبيبة: ***رباب عبد السلام نشأت محرم***

(بكالوريوس طب وجراحة)

معهد الأمراض المتوطنة وأمراض الكبد

توطئة لنيل درجة الماجستير

في الأمراض المتوطنة

السادة المشرفون

الأستاذ الدكتور : ***أشرف عمر عبد العزيز***

أستاذ بقسم الأمراض المتوطنة

كلية الطب ، جامعة القاهرة

الأستاذ الدكتور: ***عبد الرحمن نبوي ذكري***

أستاذ بقسم البيولوجي والمناعة بمعهد الأورام

جامعة القاهرة

الدكتور : ***هشام ابراهيم المخزنجي***

مدرس بقسم الأمراض المتوطنة

كلية الطب ، جامعة القاهرة

كلية الطب

جامعة القاهرة

2008

Abstract

Hepatocellular carcinoma (HCC) is the third largest cause of cancer deaths worldwide and chronic HCV infection is considered one of the most important risk factor for HCC, representing about 25% of HCC cases.

The early detection of Hepatocellular carcinoma in an at-risk population is the only hope to provide the effective treatment and to reduce the death rate. Many trials were done to use new screening serum markers instead of serum level of alpha-fetoprotein which are commonly used in combination with abdominal ultrasonography, because it is associated with high rate of both false positive and negative results.

In this study, genetic differences of IFN-receptor gene family (IFN-1, IFN-3 and IFN-7) was studied in hepatitis C cirrhotic patients who developed hepatocellular carcinoma from those who did not and we used the expression profile of IFN-receptor gene family to detect HCC as early as possible while screening hepatitis C cirrhotic patients.

Key words: HCC; hepatocellular carcinoma, HCV; hepatitis C virus, IFN-R; interferon receptor.

AKNOLEDGMENT

I am indebted to my supervisors:

*Prof. Dr**: Ashraf Omar Abdel-Aziz,*** **Professor of Tropical Medicine in Faculty of Medicine, Cairo University**

*Prof. Dr**: Abdel- Rahman Nabawi Zekri,*** **Professor of Tumor Biology in National Institute of Cancer, Cairo University**

*And Dr**: Hesham Ibrahim Al-Makhzangy,*** **Lecturer in Tropical Medicine in**
Faculty of Medicine, Cairo University

For their generous contributions and great effort in completing this work

I am so grateful to my parents for their continuous encouragement and support to complete this thesis

I particularly appreciate my husband for his effort & motivation to do my Best

Contents

LIST OF ABBREVIATIONS

- ***Cm:*** Centimeter = 0.01 meter.
- ***dl:*** 0.1 liter = 100 cc.
- ***Fig.:*** Figure.
- ***mg:*** Milligram = 0.001 gram
- ***ml:*** Milliliter.
- ***No:*** Number
- ***Ng:*** Nano gram.
- ***µg (mcg):*** Micro gram = 0.000001 gram.

- ***AFP:*** Alpha feto protine.
- ***AFU:*** Alpha-L-fucosidase.
- ***AFB1:*** Aflatoxin B1.
- ***ALP:*** Alkaline phosphatase.
- ***ALT:*** Alanine transaminases.
- ***ASR:*** Age-standardized incidence rate.
- ***AST:*** Aspartate aminotransferase.
- ***CBC:*** Complete blood count.
- ***c-DNA:*** cyclic- DNA.
- ***CLDs:*** Chronic liver diseases.
- ***CT (or CAT) scans:*** Computed axial tomography.
- ***DCP:*** Des-gamma-carboxyprothrombin.
- ***HB:*** Hemoglobin.
- ***HBV:*** Hepatitis B virus.
- ***HBsAg:*** Hepatitis B- surface antigen.
- ***HBe-Ag:*** Hepatitis B- envelope antigen.
- ***HCC:*** Hepatocellular carcinoma.
- ***HCV:*** Hepatitis C virus.
- ***HCV-Ab:*** Hepatitis C virus- antibodies.
- ***HENCORE group:*** Hepatitis C European Network for C-operative Research group.
- ***HIV:*** Human immune deficiency virus.
- ***IgM:*** Immunoglobulin M.
- ***IFN:*** Interferons**.**
- ***IFNR:*** IFN receptor.
- ***IVDU:*** Intravenous drug users.
- ***MCC:*** Modified Child-Pough classification.
- ***MECC:*** Medical epidemiology cancer center.
- ***MRI:*** Magnetic resonance imaging.
- ***NS:*** Nonstructural proteins.
- ***5'-NPD:*** 5'-nucleotide phospho-diesterase

- ***PAT:*** Parenteral anti-schistosomal therapy.
- ***PCR:*** Polymerase chain reaction.
- ***PBMCs***: peripheral blood mononuclear cells.
- ***PGCP:*** Plasma glutamate carboxy-peptidase.
- ***PSC:*** Primary sclerosing cholangitis.
- ***PT:*** Prothrombin time.
- ***PC:*** Prothrombin concentration.
- ***RACK-1:*** Receptor for activated C-kinase.
- ***REDS:*** Retrovirus Epidemiology Donor Study.
- ***RT-PCR:*** Reverse transcriptase- Polymerase chain reaction.
- ***SCCA:*** Squamous cell carcinoma antigen.
- ***TGF-α1:*** Tumor growth factor alpha1.
- ***US:*** Ultrasound.
- ***VEGF :*** Vascular endothelial growth factors

LIST OF TABLES AND FIGURES

List of figures of review

List of figures of results

List of tables of results

Introduction

Hepatocellular carcinoma (HCC) represents 80-90% of primary liver malignancies and is the third largest cause of cancer deaths worldwide ***(Parkin, et al 2001)*** with over 1.3 million cases annually ***(Peterson, et al 2000)***. It is the fifth most common cancer in men and the ninth in women ***(El Serag, 2002).***

In Egypt, HCC is the third most common cancer for males and is the forth in females ***(Globocan 2001).*** Male predominance was marked with a 3.8:1 male-to-female ratio and most patients have underline cirrhosis or shistosomiasis. It is more prevalent among old age groups than younger age groups ***(El Zayadi, et al 2001).***

The most important risk factors for HCC at a global level are chronic HBV infection, chronic HCV infection, both representing between 70% and 95% of patients ***(Lok, et al 2001)*** and cirrhosis representing between 60% and 80% of patients ***(Sangiovanni, et al 2004).***

There is an apparent increase in the number of HCC patients among Egyptians which may be explained by the increase in prevalence of HCV, exposure to variable carcinogens, survival rate of cirrhotic patient which giving a chance for development of HCC and usage of new techniques for early detection of HCC ***(Shamaa, et al 1992).***

HCC carries a grave prognosis as the majority of patients is diagnosed at the advanced stage and is therefore precluded from radical treatments. Almost all patients will die within 1 year after diagnosis and five-year survival is between 2% and 6% ***(Arii, et al 2000).*** Therefore, the only hope for effective treatment lies in early detection, or screening of an at-risk population {patients with chronic viral hepatitis (hepatitis B or hepatitis C) or with cirrhosis} which may reduce death rate ***(Sangiovanni, et al 2004).***

There are two tests commonly used to screen for liver cancer, namely ultrasound examination of the liver and serum level of alpha-fetoprotein due to the cost-effectiveness ***(Daniele, et al 2004)***. However, both tests have disadvantages. Serum AFP is not very accurate as its predictive accuracy for HCC is only about 15% and its diagnostic sensitivity ranges from 39% to 64% ***(Soresi, et al 2003, Daniele, et al 2004)***. Also, Ultrasound sensitivity is low as its accuracy is operator dependent and in the presence of cirrhosis becomes even less reliable, missing a significant number of cancers ***(Teefey, et al 2003).***

Recently, new serum screening markers are under evaluation to be used in early detection and diagnosis of HCC. They currently are research tools and not generally available. They could be very helpful in diagnosing more cases of HCC when used in conjunction with AFP, than with AFP alone. For example; α-Fucosyl-transferase, alpha-L-fucosidase and vascular endothelial growth factors ***(Motawa, et al 2005)***.

Aim of the work

The aim of the work is to study genetic differences of IFN-receptor gene family (IFN-1, IFN-3&IFN-7) in hepatitis C cirrhotic patients who developed hepatocellular carcinoma from those who did not, as there is a gap in the literatures and using the expression profile of IFN-receptor gene family to detect HCC as early as possible while screening hepatitis C cirrhotic patients.

Patients and Methods

This study was conducted on 90 patients who attended to the National Hepatology and Tropical Medicine Research Institute (N.H.T.M.R.I). They were of both sexes (75 males and 15 females) and their ages ranged from 25 to 76 years.

They were divided into three groups. Group I included thirty patients [25 males (83.33%) and 5 females (16.67%)] with HCV infection alone. Group II included thirty patients [22 males (73.33%) and 8 females (26.67%)] with liver cirrhosis on top of HCV infection evident by abdominal sonography. Group III included thirty HCC patients on top of HCV cirrhosis [28 males (93.33%) and 2 females (6.67%)] evident by triphasic spiral CT and elevated serum AFP > 100 μg/L.

Patients, who had HBV infection and other chronic liver diseases, were excluded from our study. All patients were subjected to thorough history taking, full clinical examination, routine laboratory investigations, viral markers for HCV and HBV, serum AFP, abdominal ultrasonography and triphasic spiral CT which was done only for group III. Blood samples were collected from all cases for expression profile of the interferon receptor gene family on the peripheral blood lymphocytes.