Serum LINE-1 hypomethylation as diagnostic marker for hepatocellular carcinoma

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ABSTRACT

Back ground: Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world with a 5 year survival rate of less than 5% and an incidence of at least one million new patients per year.

Incidence of HCC in Egypt is currently increasing, which may be the result of a shift in the relative importance of HBV and HCV as primary risk factors.

Objective: The aim of this work is to assess use of serum LINE-1 hypomethylation as a diagnostic and prognostic marker for HCC.

Methods: The present study was performed on ninety patients and 10 healthy subjects; fifty patients had hepatocellular carcinoma, twenty patients had liver cirrhosis and twenty patients had chronic hepatitis C.

Serum LINE-1 hypomethylation measurement was performed including DNA preparation and measurement of hypomethylation

Results:

-Serum LINE-1 hypomethylation was a statistically highly significant ($p< 0.01$) in HCC group when compared with the control groups.

- At cut off value of 60 nmol/l (Best cut off) Serum LINE-1 hypomethylation yields a sensitivity, specificity, positive predictive value and negative predictive values of 46%, 95%, 95.83%, and 41.30 respectively.

Hypomethylation values is significantly higher in multiple tumors, Tumor size 5 or > 5cm, and in patients with PVT than in single tumors, Tumor size <5 cm and patients with no PVT.

CONCLUSION

Serum LINE-1 hypomethylation can serve as prognostic marker of HCC.
Serum LINE-1 hypomethylation is more valuable than alpha fetoprotein as a prognostic marker of HCC.

Key Words: HCC, Serum LINE-1 hypomethylation.

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LIST OF ABBREVIATIONS

AFB1	: Aflatoxin B1
AFP	: Alpha fetoprotein.
AFPIC	: Alpha fetoprotein Immunocomplexes.
AFU	Alpha-1- Fucosidase
ALT	: Alanine Transaminase
Anti-HBe	: Hepatitis B virus hidden antibodies
bp	: base pairs
CEA	:Carcinoembryonic antigen
CEUS	:Contrast enhanced ultrasound
CIMP	:Cytosine phosphoguanine Island Methylator Phenotype
CIN	:Chromosomal Instability
COBRA	:combined bisulfite restriction analysis
CPG	: Cytosine phosphoguanine dinucleotides
CT	: Computed Tomography
CTAP	:CT arterioportography
CT antigens	: Cancer Testis antigens
CTL	:Cytotoxic T cells
DCP	:Desgammacarboxyprothrombin
DNA	: Deoxy ribonucleic acid
DNMTs	: DNA methyl Transferases
DUS	: Doppler ultrasound
E-Cadherin	: Epithelial calcium dependent adhesion molecules
FI-F4	: Degrees of liver fibrosis
GAGHCC	:Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis
GGT	Gamma glutamyl transferase
GP73	Golgi protein 73
GPC3	Glypican-3
HBe Ag	Hepatitis B virus hidden antigen
HBs Ag	Hepatitis B virus surface antigen
HBV	Hepatitis B virus

HCC : Hepatocellular Carcinoma
HCV Hepatitis C virus
HGF : Hepatocyte growth factor
HR : High risk
hTERT : Human telomerase reverse transcriptase
IL-8 : Interleukin-8
IOUS : Intraoperative ultrasound
Kb : Kilo base
LINE-1 : Long interspersed nuclear element
LCA : Lectin Lens Culinaris agglutin
MAGE : Melanoma antigen gene
MBDs : Methyl CPG binding proteins
5-mc : 5- methyl cytosine
MINT : Methylated in Tumor
MLH 1 : Mutl homolog 1
MRI : Magnetic Resonance Imaging
m RNA : Messenger ribonucleic acid
ORF : Open reading frame
P53 : Protein 53
PBMC : peripheral blood mononuclear cells
PC : Prothrombin Concentration
PCR : Polymerase Chain Reaction
PET : Positron Emission Tomography
PIVKA : Prothrombin induced by vitamin K absence
PPV : Positive predictive value
PT : Prothrombin Time
RIZ 1 : Retinoblastoma protein interacting zinc finger gene
RNA : Ribonucleic acid
RTPCR : Reverse transcription PCR
SACE : Serum angiotensin converting enzyme
SCCA : Squamous cell carcinoma antigen
SCCAIC : Squamous cell carcinoma antigen Immunocomplexes.
SOCS 1 : Suppressor of cytokine signaling 1
SSX-2 : Synovial sarcoma x break point 2

TGF-B1 :Transforming growth factor beta 1
THI :Tissue harmonic imaging
TSA : Total sialic acid
TSG :Tumor suppressor gene
TSGF : Tumor specific growth factor
ULN : upper limit of normal
VCAM-1 :Vascular cell adhesion molecules
VEGF :Vascular endothelial growth factor

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world with a 5 year survival rate of less than 5% and an incidence of at least one million new patients per year. (Bruix et al., 2004).

HCC incidence rate has been increasing over the last two decades of the 20th century. In the United States, the reported incidence has increased to 4.7/100,000. The male population, both black and white, is primarily affected. However, the incidence of HCC in eastern Asia and middle Africa is more than five times that of North America. Furthermore, from 1981 to 1985 the peak incidence of HCC occurred in patients 80 to 84 years of age, whereas from 1991 to 1995 the peak was noted in persons 74 to 79 years of age. This shift in incidence toward younger persons seen over the last two decades coincides with the prevalence of the hepatitis C Virus infection. (Jorge and Marrero, 2003)

Incidence of HCC in Egypt is currently increasing, which may be the result of a shift in the relative importance of HBV and HCV as primary risk factors. HCC is the second most frequent cause of cancer incidence and mortality among men in Egypt. Hospital based studies from Egypt have reported an increase in the relative frequency of all liver-related cancers in Egypt (>95% as HCC), from _4.0% in 1993 to 7.3% in 2003. (El-Zayadi et al.,2005)