The Role of Procalcitonin in Diagnosis of Bacterial Infection in Hepatocellular Carcinoma Patients After Trans Arterial Chemoembolization

Thesis

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List of Abbreviations (Cont.)

Abbrev.	Full term
PVE	Portal vein embolization
RCTs	Randomized controlled trial study
RFA	Radiofrequency ablation
RFTA	Radifrquency thermal ablation
RILD	Radiation induced liver disease
RT-PCR	Reverse-transcriptase polymerase chain reaction
SCCA	Squamous cell carcinoma antigen
SHARP	Sorafenip HCC Assessment Randomized protocol
ShRNA	Short hairpin RNA
SiRNA	Small interfering RNA
SIRT	Selective internal radiation therapy
TA-4	Tumor associated antigen
TAC	Transarterial Chemotherapy
TACE	Transarterial Chemoembolization
TAE	Transarterial embolization
TARE	Transarterial radioembolization
TGF	Transforming growth factor
TGF-B1	Transforming growth factor B1
TLS	Tumor lysis syndrome
TNM staging	Tumor node metastasis staging
UICC	Union International Centre de Cancer
VEGF	Vascular endothelial growth factor PEI Percutaneous ethanol injection
PEIT	Percutaneous ethanol injection treatment
PI3K	Phosphoinositide 3-kinase
PIVKAII	Prothrombin induced by vitamin K absence II
PLAT	Percutaneous Laser ablation Thermotherapy
PMCT	Percutaneous microwave thermotherapy
PUO	Pyrexia of unknown origin
PVA	Polyvenyle alcohol HS-AFP Hepatoma specific Alpha fetoprotein
HSPS	Heat shock protein
HSV-tk	Herpes simplex virus thymidine kinase
hTERT	Human telomerase reverse transcriptase
ICG	Indocyanine green
Ics	Immune complexes
IFN	Interferon
IGF	Insulin-like growth factor
IGF-2	Insulin growth factor-II

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Moataz Ahmed Hasan

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List of Abbreviations

Abbrev.	Full term
^{90}Y	Yatrium 90
AASLD	American association for study of liver disease
AFP	Alpha fetoprotein
AFU	Alpha L-Fucosidase
BCLC staging	Barcelona Clinic Liver Cancer staging
BMSC	Bone marrow mononuclear stem cell
CCC	Cholangiocarcinoma
CD	Cytosine deaminase
CEA	Carcinoemberyonic antigen
CLD	Chronic liver Disease
CLIP staging	Cancer of liver Italian program staging
CLIP	Cancer liver Italian program
CT	Computed Tomography
CTA	CT arteriography
CTAP	CT arterioportography
DCP	Des-gama-carboxy prothrombin
dsRNA	Double stranded RNA
DUS	Doppler Ultrasound
ECLIA	Electrochilu-minescence immunoassay
EGF	Epidermal growth factor
EPA	Environmental protection Agency
ERK	Extracellular signal-regulated kinase
EUS	Endoscopic ultrasonography
FNH	Focal nodular hyperplasia
FUDR	Fluorodeoxyuridine
GCV	Ganciclovir
GGT	Gama glutamyl transferase
GPC3	Glypican-3
GRE	Gradient recall echo
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HIFU	High intensity focus ultrasound

List of Abbreviations (Cont.)

Abbrev.	Full term
IL-8	Interleukin-8
ILA	interstitial laser ablation
ILP	Interstitial laser Photocoagulation
IOUS	Intra-operative ultrasonography
LA	Laser ablation
LAK cells	Lymphokine activated killer cells
LC-705	Lactobacillus rhamnosus
LCA	Lens culinaris agglutinin
LDH	Lactat dehydrogenase
LDLT	Living donner liver transplantation
LITT	Laser induced thermotherapy
LT	Liver Transplantation
L-TAC	Transarterial chemotherapy, lipidolization TAC+E: Transarterial chemotherapy and particle embolization
L-TAC+E	Transarterial chemotherapy, lipidolization and particle embolization
MAGE-1	Melanoma antigen gene
MAPK	Mitomycin-activated protein kinase
mCRC	Metastatic colorectal Cancer
MDCT	Multi-detector CT
MELD	Model for end stage liver disease
MOVC	Membranous obstruction of inferior vena cava
mRNA	microRNA
MSCT	Multi-slice CT
mTOR	Mammalian target of rapamycin
MWA	Microwave ablation
NAFLD	Non alcoholic liver disease
NRH	Nodular regenerative hyperplasia
NSAIDS	Nonsteroidal anti-inflammatory drugs
OLT	Orthotopic liver transplantation
OS	Overall survival
P CEA	Polyclonal carcino-embryonic antigen
P53	Tumuor suppressor gene
PAAI or PAI	Percutaneous acetic acid Injection
PDGF	Platelet-derived growth factor

INTRODUCTION

Procalcitonin (PCT), the precursor of the hormone calcitonin, is produced under normal conditions in the C cells of the thyroid gland. In healthy subjects, PCT levels are <0.10 ng/ml. PCT determination was first performed in 1993 in children to differentiate bacterial from viral meningitis ***(Assicot et al., 1993)***.

Since that date, PCT has become a marker of bacterial infection and there is a widening range of indications for its use ***(Ferriere, 2000 & Schwarz et al., 2000)***.

Procalcitonin is a 116 amino acid peptide with a sequence identical to that of the prohormone of calcitonin ***(Le Moullec et al., 1984)***. But PCT itself has no known hormonal activity. Under normal metabolic conditions, PCT is only present in the C cell of the thyroid gland. In bacterial infection and sepsis its level increase in the serum; however, intact PCT is found in the blood and, more importantly, its level is related to the severity of sepsis ***(De Werra et al., 1997& Ugarte et al., 1999)***.

The origin of inflammatory synthesis of PCT has not been clarified yet, neuroendocrine cells of different organs (lung, intestine, kidney, pancreas, adrenal gland, and more recently the liver) have been proposed as a major source of PCT production ***(Morgenthaler et al., 2003).***

Determination of the PCT level is now routinely performed in intensive care and surgery units to provide rapid evidence of bacterial origin of a shock or a respiratory distress syndrome; to differentiate pancreatitis with infected necrosis more easily from non-complicated pancreatitis; and for early detection of infectious postoperative complications ***(De Werra et al., 1997& Reith et al., 1998)***.

Several meta-analyses concluded that in critically ill patients, PCT is superior to C-reactive protein (CRP) for diagnosing bacterial infections (Lim et al., 2003). PCT has been proposed as a marker of bacterial infection in critically ill patients ***(Ugarte et al., 1999 & Muller et aL., 2000)***.

Post-ablation and Embolization Syndrome

This syndrome is a transient self limiting symptom or sign complex of low-grade fever and general malaise ***(Lee et al., 1997)***. The duration depends on the volume of necrosis produced and the overall condition of the patient. If small areas are treated, the patient is unlikely to experience post-ablation syndrome at all. If very large areas of liver tumors are ablated, the syndrome may persist for 2 to 3 weeks. The majority of patients who have this syndrome will experience some malaise for 2 to 7 days depending on the volume of tumor and surrounding tissue ablated and the integrity of the patient's immune system (i.e. patients being treated with steroids or those who have small tumors may experience post ablation syndrome) ***(Chopra , 2000)***.

The procedure is generally well tolerated, with major complications in only 4-7% of procedures and a 30-day mortality of approximately 1% (Sakamoto et al., 1998). However, the procedure has been associated with several complications such as acute hepatic failure (2.6% of cases), liver infarction (0.3%), hepatic biloma formation (0.8%), liver abscess (0-1.4%), or septicemia (2.6-11%) ***(Chung et al., 1996)***. A standard antibiotic regimen with cephalosporin and levofloxacin has been used for prophylaxis against such post-procedural infectious complications ***(Geschwind et al., 2002)***.

AIM OF THE WORK

To study the value of serum procalcitonin in diagnosis of bacterial infection in hepatocellular carcinoma patients after Trans arterial chemoembolization.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor worldwide, with an increasing global annual incidence ***(Hussain et al., 2008).***

Hepatocellular carcinoma (HCC) is generally occurring in association with cirrhosis, particularly due to hepatitis C, hepatitis B, alcohol, hereditary hemochromatosis, and primary biliary cirrhosis ***(Bruix and Sherman, 2005).*** There is a continuously increasing trend of HCC in Egypt ***(Shaker et al., 2011***). Liver cancer is the sixth most common cancer (749,000 new cases), the third cause of cancer related death (692,000 cases), and accounts for 7% of all cancers HCC represents more than 90% of primary liver cancers and is a major global health problem ***(Eurobean assosiation of study of liver disease (EASL), 2012).***

El-Zayadi et al.(2001) reported that, in Egypt, 4.7% of chronic liver disease patients suffer from HCC. The development of HCC is mainly due to high rates of hepatitis B and C infections among Egyptian patients.In 2005 the authors reported increase of HCC among chronic liver disease patients up to 7.2% ***(El-Zayadi et al., 2005).***

The risk of developing of HCC for a patient with HCV-related cirrhosis is approximately 2-6% per year ***(Sangiovanni et al., 2004).*** But it usually develops in an already damaged, often cirrhotic liver ***(Masuzaki and Omata, 2008).*** So screening should be applied to those patients ***(Ryder, 2003a).*** While

Patients with chronic hepatitis B virus infection are known to be at risk for HCC even without cirrhosis, so all patients with chronic HBV (those who are HBsAg +ve) should be considered for screening for HCC ***(Lok &Mcmahon, 2001).***

The incidence of HCC generally increases with age, although there are geographic differences. The majority of patients are 40–60 years old with a peak incidence in the eighth decade ***(Goodman, 2007).***

HCC is a multi-stage disease whose occurrence is linked to environmental and life style factors. The great variations in levels of carcinogenic factors in the environment account for the different incidences of the tumor ***(Ikai et al., 2004).***

Regardless of geographic location, HCC occurs more frequently in men than women, with (male to female) ratios in various countries ranging from (2:1 to 5:1) ***(Goodman, 2007).***

This malignancy is becoming recognized as an early complication and the most frequent cause of death in persons with viral-associated cirrhosis ***(Benvegnù et al., 2004)***

Optimal care of the patient with HCC is best achieved through referral to a multidisciplinary team of hepatologists, transplant and hepatobiliary surgeons, interventional radiologists, and oncologists. The therapeutic plan should follow **EASL 2012** practice guidelines for the management of HCC, taking into consideration the different treatment modalities, including resection, liver transplantation, local ablative therapies, and chemotherapy ***(EASL, 2012)***.