Clinical Utility of Serum Hepatocyte Growth Factor in Diagnosis of Hepatocellular Carcinoma

Thesis

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Rehab Hamdy Hafez


To
My Family

INTRODUCTION

Hepatocellular Carcinoma **(**HCC) represents the fifth most common cancer in the world and the third most frequent cause of mortality among oncological patients. It is responsible for 500,000 deaths globally every year. It represents the most common primary malignant tumor of the liver. Its incidence is increasing because of hepatitis B and C virus infections, and it is one of the major causes of death among patients with cirrhosis ***(Jemal et al., 2011).***

In 2001, HCC in Egypt was reported to account for about 4.7% of chronic liver disease patients. In another study a remarkable increase from 4-7.2% was reported over a decade ***(Hussein et al., 2010).*** In Egypt, HCC is third among cancers in men with more than 8,000 new cases predicted by 2012.The HCC epidemic in Egypt is associated with hepatitis C viral infection (HCV). Egypt has the highest prevalence of HCV in the world with 13.8% of the population infected and seven million with chronic HCV liver disease. Up to 90% of HCC cases in the Egyptian population were attributed to HCV ***(Amr et al., 2010)***.

The prognosis of HCC remains poor, and most patients have a five years survival rate of less than 5% mainly because of late diagnosis ***(Lei et al., 2010)***.

Early detection of HCC opens doors for various effective treatments such as surgical resection, radiofrequency ablation, and transplantation, which can subsequently lead to long-term survivals in a great number of HCC patients ***(Kim et al., 2010).***

Early detection is possible with ultrasound scanning and AFP monitoring, although the use of AFP as a screening test is complicated by frequent false positive and false negative results.

The sensitivities and specificities of serum AFP for the detection of HCC in HCV-related liver cirrhosis were 72.7% and 59.7% for AFP more than 20 ng/mL respectively and 47.3% and 92.5% for AFP more than 100 ng/mL respectively ***(Kim et al., 2006).***

In addition, AFP serum concentrations do not correlate well with the prognostic parameters of HCC such as tumor size, stage, or disease progression. Ethnic variability may also exist. Furthermore, in some cases of HCC, AFP elevations are not apparent at all ***(Tara and Sitki, 2012)***. Besides, serum AFP levels are frequently not elevated at a significant proportion in patients with early-stage potentially curable HCC. Therefore, other markers should have been studied in an attempt to identify a more sensitive laboratory test ***(Abdel-Rahman et al., 2010)***.

Hepatocyte growth factor (HGF) regulates cell growth, cell motility, and morphogenesis by activating a tyrosine kinase signaling cascade after binding to the proto-oncogenic c-Met receptor. Hepatocyte growth factor is secreted by mesenchymal

cells and acts as a multi-functional cytokine on cells of epithelial origin. Its ability to stimulate mitogenesis, cell motility, and matrix invasion gives it a central role in angiogenesis, tumorogenesis, and tissue regeneration. It is secreted as a single inactive polypeptide and is cleaved by serine proteases into a 69-kDa alpha-chain and 34-kDa beta-chain. A disulfide bond between the alpha and beta chains produces the active heterodimeric molecule ***(Michael and George, 2012).***

AIM OF THE WORK

The aim of this study is to evaluate the clinical utility of serum HGF as a non invasive biomarker in diagnosis of hepatocellular carcinoma, and to correlate its levels with serum levels of AFP, the routinely used serological test in diagnosis of HCC.

CHAPTER II
HEPATOCELLULAR CARCINOMA

A. Epidemiology of HCC:

1. Geographic Distribution:

Hepatocellular Carcinoma **(**HCC) represents the fifth most common cancer in the world and the third most frequent cause of mortality among oncological patients. It is responsible for 500,000 deaths globally every year. It represents the most common primary malignant tumor of the liver. Its incidence is increasing because of hepatitis B and C virus infections, and it is one of the major causes of death among patients with cirrhosis ***(Jemal et al., 2011).***

Approximately 75% to 80% of cases of HCC occur in Asia. In the USA, HCC is much less common than in other parts of the world and accounts for only about 16,000 or 2.9% of cancer deaths annually ***(Davis et al., 2008).***

Egypt has the highest prevalence of hepatitis C virus worldwide (13.8%) and has rising rates of HCC. HCC has the second most frequent incidence and mortality among men in Egypt. Hospital-based studies in Egypt have reported an increase in the relative frequency of all liver-related cancers (95% as HCC), from 4% in 1993 to 7.3% in 2003 ***(Lehan and Wilson, 2009).***

The prevalence of HCC is high in Nile Delta, and is more common in males, rural residents and farmers especially in HCV and HBV patients. In rural areas there are other risk factors such as aflatoxin (AF), cigarette smoking, occupational exposure to chemicals such as pesticides and endemic infections in the community, like Schistosomiasis ***(Abdel-hamid, 2008 and Anwar et al., 2008).***

2. Age and Sex:

Age at diagnosis varies widely according to geographic distribution. Diagnosis of HCC at younger age reflects the history of HBV and HCV infections ***(Winter, 2006).*** Worldwide, there is a clear predominance in males, with male to female ratio ranging from 1.5: 1 in countries with a low incidence of HCC to approximately 3: 1 in populations with a high frequency ***(El-Serag and Rudolph, 2007; Umemura et al., 2009)***.

In Egypt the mean age is 54±9 years, with high prevalence between 51 and 60 years. Male to female ratio was 5:1. Farmers constituted 37.6%, workers 22.9% and housewives 12.8% of the patients ***(Abdel-Wahab et al., 2007).***

B. Risk Factors:

Any cause of liver disease that can result in cirrhosis should be considered a potential risk factor for HCC. Not surprisingly the most common causes of cirrhosis, namely HBV, HCV and alcohol, are also the most common causes of HCC (Figure 1) ***(Davis et al., 2008).***