New Modalities in Treatment of Hepatocellular Carcinoma

Essay

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In Tropical Medicine

By

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor woldside, with an increasing global annual incidence ***(Hussain et al., 2001).***

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).*** 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 American Association for the Study of Liver Disease (AASLD) practice guidelines for the management of HCC, taking into consideration the different treatment modalities, including resection, liver transplantion, local ablative therapies, and chemotherapy ***(Bruix and Sherman, 2005).***

Alternative non-surgical methods [percutaneous local ablative therapy (PLAT)] include transarterial chemo-embolization (TACE) ***(Lo et al., 2002)*** and percutaneous ultrasound-guided ablation therapy including injection of ethanol ***(Huo et al., 2002)*** or acetic acid ***(Huo et al., 2003a)*** and radio-frequency thermal ablation ***(Livraghi et al., 1999).***

Percutaneous local ablative therapy (PLAT) is indicated for patients with small HCC (<5 cm) confined to the liver that is unresectable due to limited liver reserve or compromised liver function. It is usually done through the percutaneous route under ultrasound or computed tomography guidance. The technique is difficult for patients with multiple tumors (more than three) because of the need for repeated puncture ***(Lau et al., 2003).***

Percutaneous ethanol injection (PEI) has been shown to produce necrosis of small HCC. It is best suited to peripheral lesions, less than 3 cm in diameter. Radiofrequency ablation may be a good alternative ablative therapy ***(Ryder, 2003).***

The efficacy of PEI is limited by the presence of septa in the tumor nodule, which prevents uniform diffusion of ethanol and necessitates repeated treatment sessions. Further, capsular invasion cannot be ablated because ethanol cannot dissolve the fibrous capsule. Percutaneous acetic acid injection (PAI) has been used as an alternative ***(Ohnishi et al., 1994).***

Percutaneous ablation using acetic acid is an attractive method because of its low morbidity and low number of sessions required to induce complete tumor necrosis ***(Fartoux et al., 2005).***

The major limitation for percutaneous injection therapy is that it is indicated only for small (<3 or 4 cm) HCC nodules ***(Huo et al., 2003b).***

Aim of the Work

To discuss different new modalities in treatment of hepatocellular carcinoma (HCC).

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Resection is the treatment of choice for HCC in non-cirrhotic patients ***(Bralet et al., 2000)***.While in cirrhotic patients the preoperative liver functional reserve assessment is critical for patient selection ***(Makuuchi & Sano, 2004)***.

Liver transplantation has been claimed to simultaneously cure the malignant disease and replace the premalignant cirrhotic liver ***(Tanaka, 2004)*** which is responsible for both postoperative hepatic failure and tumor recurrence after partial hepatic resection ***(Lo and Fan, 2004).***

Aim of the Work

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Epidemiology of Hepatocellular Carcinoma

National cancer registry reported that hepatocellular carcinoma is one of the most common three cancers in Egypt being, cancer bladder, breast cancer, and hepatocellular carcinoma ***(NCR, 2002).*** 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 ***(El-Zayadi et al., 2001).*** And in more recent study it reach7.2% ***(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 only to those patients ***(Ryder, 2003).*** 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 et al., 2001).***

Cirrhosis may be caused by viral hepatitis (primarily hepatitis B and C), alcohol, hereditary haemochromatosis, autoimmune liver diseases and actually any disease that results in chronic inflammation of the liver ***(Martin and Dufour, 2008).***While from global perspective, the two most important risk factors for HCC are chronic hepatitis B and C infection ***(But et al., 2008).***

The incidence of HCC generally increases with age, although there are geographic differences. The majority of patients are 40–60 years old ***(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).***

Etiology of Hepatocellular Carcinoma

Pathogenesis is multifactorial, enviromental, infectious, nutritional, metabolic and endocrine factors contribute directly and indirectly to hepatocarcinogenesis ***(Rochen and Geracth, 2001)***

A-Infectious Factors:

I-Viral:

1-Role of HBV:

The prevalence of HBV was declining over the last two decades ***(El-Zayadi et al., 2005)*** because of the increasing utilization of HBV immunization ***(Liu and Kao, 2007).***

Mechanisms of carcinogenesis:

i. Necroinflamation: Still among the proposed theories for HBV induced hepatocarcinogenesis is that cirrhotic remodeling alone is a major risk factor for the initiation of malignant transformation ***(Bailey and Brunt, 2003).***

ii. Viralprotien: The virus may have some direct carcinogenic properties itself ***(Geissler et al., 1997).***

iii. HBV genotype: In Asia, genotype C is found to be commonly associated with more severe liver disease, cirrhosis and the development of HCC, compared to genotype B whereas in Western Europe and North America, genotype D is more associated with severe liver disease and a higher incidence of HCC, than genotype A ***(Liu and Kao, 2007).***

2-Role of HCV:

El-Zayadi et al., (2005) reported that 87.9% of their Egyptian studied HCC patients had HCV Ab. HCV appears to play a major role in the evolution of chronic liver disease to

HCC.

Continuous inflammation and hepatocyte regeneration in the setting of chronic hepatitis and subsequent progression to cirrhosis is thought to lead to chromosomal damage and possibly to initiate hepatic carcinogenesis ***(Suruki et al., 2006).***

3-Coinfection of HBV and HCV:

HBV acts as a cofactor in the development of HCV related cirrhosis and HCC, so vaccination of patients with chronic hepatitis C against HBV has been recommended aiming to avoid further liver injury ***(Michielsen et al., 2005).***

4-Coinfection with HDV:

A study showed that HBsAg positive patients with HDV superinfection develop cirrhosis and HCC at an earlier stage (mean age 48 years), compared to HBsAg carriers without HDV infection (mean age 62 years) ***(Michielsen et al., 2005).***

5-Coinfection with HIV:

Chronic hepatitis C is more aggressive in HIV positive subjects, leading to cirrhosis and liver failure and development of HCC in a shorter time period ***(Michielsen et al., 2005).***

II-Parazite:

Schistosmiasis:

Schistosomiasis induces immune suppression, which could result in increased persistence viraemia, following acute infection of either hepatitis B or C ***(Ezzat et al., 2005),*** and consequently increased the severity of HBV infection and elevated the risk of HCC over that associated with the HBV

infection alone ***(Badawi and Michael, 1999)*** or HCV infection alone ***(El-Koby, 2000).***

B-Liver Cirrhosis:

The possible hypothesis of developing of HCC in cirrhotic liver is that, dysplastic nodules which developed within the cirrhotic liver are suspected to be the premalignant lesions of HCC ***(Theise, 1996).***

C-Toxic Factors:

I-Toxins:

1-role of alcohol:

Alcohol is of very little evidence that is directly carcinogenic or genotoxic ***(Goodman, 2007)*** but it acts as a co-carcinogen and has strong synergistic effects with other carcinogens including hepatitis B, hepatitis C, obesity and diabetes mellitus and usually occurs in the setting of cirrhosis ***(Voigt, 2005).***

2-Tobacco:

The International Agency for Research on Cancer classified smoking as a cause of hepatocellular carcinoma ***(IARC, 2004),*** Heavy smokers accumulate excess iron in hepatocytes which induces fibrosis and favors development of HCC ***(El-Zayadi et al., 2002).***

3- Aflatoxin:

Areas with high exposure of AFB1 coincide with areas with a high prevalence of HCC ***(Liu et al., 2005)*** and the relative risk of HCC for individuals exposed to aflatoxins is very high ***(Johnson, 2006)*** afinding that supports a strong

epidemiologic link between the ingestion of aflatoxin and liver cancer ***(Colombo, 2003).***

4-Thorotast:

Although many of the patients with thorotrast-associated HCC have had cirrhosis, tumors have also been found in patients with non-cirrhotic livers ***(Colombo, 2003).***

5-Vinyl chloride:

It increases the risk of developing cholangiocarcinoma and hepatocellular carcinoma. It has become much less important because exposure of workers to it is strictly regulated now ***(Koike and Shiratori, 2004).***

6-Arsenic:

Chronic exposure to drinking water contaminated with naturally occurring arsenic, such as that obtained from some wells, increases the risk of hepatocellular carcinoma. This is more common in parts of East Asia and some areas of the United States ***(Koike and Shiratori, 2004).***

7- Pictiside:

An Egyptian study suggested that exposures to organophophorus and carbamate pesticides are additive risk factors to current HCV and HBV infection among rural males but no statistically significant associations between HCC and household application of pesticides were observed for urban males or females ***(Ezzat et al., 2005).***

II-Drugs:

1-Oral contraceptive (OCs):