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Etiology, natural history and treatment of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is linked to environmental, dietary and lifestyle factors. Patients with cirrhosis and chronic carriage of hepatitis B virus (HBV) are at risk for HCC at annual rates of 3%. HCC risk is particularly high in patients with evidence of cirrhosis and histological markers of increased liver cell proliferation. In addition, thrombocytopenia, prolonged prothrombin time and over 55 years of age also predict the development of HCC. Treatment options are defined according to the presence or absence of cirrhosis, number and size of tumors, and degree of hepatic decompensation. Hepatic resection is the primary intervention for these few patients with tumor but surrounding normal liver tissue and well preserved hepatic function. Under such circumstances, the cumulative 5-year survival is approximately 45%. Liver transplantation (OLT) provides long term survivals (90% at 5 years) in patients with a HCC discovered by chance as a minute nodule and of 75% in patients with viral cirrhosis and a single <5 cm tumor or fewer than three <3 cm nodes. Since liver transplantation cannot be offered to most patients with HCC, hepatic resection remains the primary therapeutic option; 5-year survival of 50% is anticipated in patients with compensated cirrhosis and <5 cm of tumor and 75% for those with moderate portal hypertension and normal serum bilirubin values. Ultrasound-guided tumor injection with absolute ethanol or tumor thermoablation with radiofrequency provide similar survival rates but with fewer complications. Whether arterial chemoembolization benefits patients with HCC remains controversial.

Keywords: Viral hepatitis; Alcohol; Abdominal ultrasound; Hepatic resection; Liver transplantation; Percutaneous interstitial treatments

1. Introduction

Hepatocellular carcinoma (HCC) ranks as the fifth most common cancer in the world, accounting for 5.4% of all human cancer cases (Ferlay et al., 1998). A low incidence (less than 3 cases per 100,000 men) is reported in Northern Europe, Australia, and Caucasian populations in North America. A high incidence (more than 30 cases per 100,000) is reported in Eastern Asia and Middle and Western Africa, where HCC ranges from 20.8 to 48 cases per 100,000 men. The incidence of HCC rose from 1.4 per 100,000 persons during the period from 1976 to 1980 to 2.4 during the period 1991–1995 in the United States. Similar incidence trends have been observed in Italy, France, UK, Canada, Australia and Japan (Bosch et al., 1999).

2. Etiology

Chronic hepatitis B virus (HBV) infection is the primary risk factor for the development of HCC in many areas of the world. In Taiwan, the risk for HCC for men chronically infected with HBV is 102 times greater than the risk for noncarriers (Beasley, 1987) and in native Alaskan male HBV infected carriers the annual incidence rate of HCC is 387/100,000 men (McMahon et al., 1990). In a study of chronic carriers of hepatitis B surface antigen (HBsAg) in Toronto, the annual incidence of HCC was 0.47% (Sherman et al., 1995). The reduction in HCC incidence observed after the start of infant vaccination program against HBV in Taiwan further corroborates the link between HBV and HCC (Chang et al., 1997). Neonatal infection with HBV has the greatest carcinogenic potential as suggested by the woodchuck hepatitis virus model (Rogler, 1990). In men, the duration of HBV infection and the severity of the underlying chronic hepatitis correlate with an increased risk of HCC. The yearly incidence of HCC was 0% in inactive carriers (de Franchis et al., 1993; Villneuve et al., 1994), approximately 0.3% in patients with chronic HBV infection and it rose to 1.5–6.6% in patients with compensated cirrhosis (Beasley et al., 1981; Liaw et al., 1986; McMahon et al., 1990; Lok et al., 1991; Tsai et al., 1997; Ikeda et al., 1998; Fattovich et al., 2000). In Africa and Asia where the HBV infection coincides also with dietary exposure to the powerful oncogenic agent, aflatoxin, HCC may develop

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frequently in a noncirrhotic liver. Several mechanisms are involved in HBV-related carcinogenesis. Chronic inflammation of the liver and increased hepatocyte proliferation are important contributing factors to the development of HCC. Whereas integration of HBV-DNA into the DNA of the host cells and interactions of HBV specific proteins with liver genes are likely to be important in both the early and late phases of carcinogenesis (Dejean and de The, 1990; IARC, 1994).

Chronic infection with the hepatitis C virus (HCV) is an important risk factor for HCC, particularly in the West hemisphere (IARC, 1994). As is the case for chronic HBV infection, the severity of hepatitis is the crucial factor that modulates the risk of developing HCC in chronic HCV carriers. The annual risk of developing HCC was 0.4% for unselected HCV carriers with persistently high ALT values, but it rose to 1.7% in patients with histological diagnosis of chronic active hepatitis and 2.5% in those with compensated cirrhosis (Benvegnù et al., 1994; Lau et al., 1996; Bruno et al., 1997; Romeo et al., 1997; Tradati et al., 1998; Shibata et al., 1998; Cacciola et al., 1999). The co-occurrence of alcohol abuse or HBV infection probably contributes to the world-wide epidemiological and clinical heterogeneity of this tumor (Kew, 1998; Cacciola et al., 1999). The pathogenic mechanisms of HCV-related hepatocarcinogenesis are poorly understood. Replicating HCV-RNA and virus-specific protein expression have been shown in HCC cells but no reverse transcriptase activity has been detected in the infected livers (Ballardini et al., 1995; Lau et al., 1996). The core protein of HCV is a likely oncogenic candidate, as accumulates in cell nuclei, suggesting that there is a putative nuclear targeting sequence in the core protein (Ravaggi et al., 1994). HCV core protein may have an important biological role in the promotion of cell growth by down-regulating human p53, thus attenuating cellular tumor suppressor functions (Ray et al., 1997). To further illustrate this association, transgenic mice expressing the HCV core gene developed HCC. In this model, hepatic steatosis develops early in life as a histological marker of chronic HCV infection (Moriya et al., 1998). Another region of the HCV genome that may have oncogenic potential is the truncated NS3 protease which can transform murine fibroblasts and result in HCC in immunodeficient male mice (Sakamuro et al., 1995).

The association between ethanol and liver cancer has been investigated wherby the hepatotoxic effect of alcohol is dose-dependent, causing cirrhosis—the apparent basis for ethanol-associated HCC (IARC, 1988). In Italy, the risk of HCC is 13 times greater in those who consume alcohol versus those who abstain (Cottone et al., 1994). Alcohol abuse has often emerged as potentiating factor in patients with HCC due to HBV (Ikeda et al., 1998) or HCV (Benvegnù et al., 1994).

Independent of other risk factors, cirrhosis is the single most important risk factor for the development of HCC. Once cirrhosis is established, the predictors of tumor development become: male sex, age, increased serum levels of alpha-fetoprotein (AFP), disease severity and high liver cell proliferation activity (Colombo et al., 1991; Donato et al., 2001). Among patients with compensated cirrhosis the annual incidence of HCC is around 3%, ranging from 5% in the patients with high liver cell proliferation to 1% for those with lower liver cell proliferation (Donato et al., 2001). When liver cell dysplasia is present, the three year cumulative incidence of HCC increased from 17 to 72% for patients with advanced cirrhosis (Ganne-Carrié et al., 1996). Finally, the risk of HCC is exceedingly high in cirrhotic patients with atypical macroregenerative nodules, i.e. focal hyperplastic nodules of cirrhotic parenchyma. In one prospective study, 25% of macroregenerative nodules progressed to HCC in 28 months, on average (Borzio et al., 1997).

Aflatoxin B1 is an important risk factor for the development of HCC in Asia and Africa (Wogan, 1999). Aflatoxin is highly mutagenic, probably through mechanisms of epoxidation resulting in covalent binding to DNA (Wogan, 1999). A specific mutation at the third base of codon 249 of the tumor-suppressor gene p53 has been described in HCC tissue. In an animal model, rats treated with aflatoxin B1 developed HCC in a dose-dependent fashion. In a transgenic mouse model (expressing integrated HBV-DNA), treatment with aflatoxin B1 enhanced the development of HCC compared to control untreated mice. Humans are exposed to aflatoxin by ingestion of contaminated food. Worldwide, the incidence of HCC parallels the prevalence of aflatoxin-contaminated food products. It is not clear whether aflatoxin independently causes HCC, or amplifies the risk created by HBV infection. A statistically significant increase in the relative risk of 3.4 for HCC with only aflatoxin biomarkers was detected in a nested case-control study of 18,000 male residents of Shanghai. The risk rose from 7 for chronic HBV carriers to 59 per 100,000 for individuals positive for both aflatoxin and HBV biomarkers (Ross et al., 1992). In China, aflatoxin exposure, as assessed by measurement of the metabolite M1 in pooled monthly urine samples, increased the relative risk for HCC by 3.3-fold (Sun et al., 1999).

Metabolic conditions associated with an increased risk of HCC include genetic hemochromatosis (GH), porphyria cutanea tarda, tyrosinemia, hypercitrullinemia, alpha-1-antitripsin (AAT) deficiency and Wilson's disease. While Glycogenosis types I and III, Wilson's disease and hereditary fructose intolerance are associated with an increased risk for the development of HCC, it is substantially lower. Cirrhotic patients with GH have an estimated probability of HCC of 30% over 10 years, 200 times higher than in the general population (Niederau et al., 1985). AAT deficiency associated homozygous AAT defect is a risk factor for HCC (Eriksson et al., 1986).

The incidence of HCC among patients with autoimmune hepatitis is low (0.2% per year). The relative pathogenic role of co-existing chronic HCV infection has not been established (Wang and Czaja, 1988; Ryder et al., 1995). Patients

with primary biliary cirrhosis have an increased risk of HCC, corresponding to a yearly incidence of 0.7% increases to 6% with stage III and IV disease (Howel et al., 1991).

There is no substantial evidence for an etiologic association between HCC and oral contraceptives (Stanford et al., 1989; MILTS, 1997). There may be an association, especially in HBsAg-negative patients, between tobacco smoking and HCC.

Thorotrast, a colloidal solution of thorium dioxide with the isotope radiothorium, was formerly used as contrast medium in radiology and has been associated with development of HCC (Doll and Peto, 1981). Hepatic tumors developed about 20 years after intravascular administration of Thorotrast. The association between HCC and exposure to vinyl chloride monomer is disputed (Greenberg et al., 2001).

3. Natural history

During the early phases of growth, the tumor is clinically indolent but becomes symptomatic in the advanced stages of disease with painful hepatomegaly and/or jaundice. HCC is first detected as a multinodular tumor at diagnosis in half of the patients with compensated cirrhosis under surveillance (Fasani et al., 1999). This HCC pattern is more common in patients with multiple etiological factors than in those with a single etiologic factor (Benvegnù et al., 2001). Multinodular HCC may be either expression of multifocal origin or expression of intrahepatic metastases of a prior tumor. It is difficult to distinguish from these alternative hypotheses and may only be possible by matching radiological and histopathological findings on explanted or resected livers. All three forms of HCC occur with cirrhosis. Based on growth patterns, HCC is classified as infiltrative, expanding, multinodular or mixed type.

The natural history of HCC may be difficult to interpret since the growth pattern varies greatly from one tumor to another, independently on etiology. The median doubling time for small tumors is 6 months (Okazaki et al., 1989). The natural history of HCC may be difficult to interpret also because some nodes have constant rates of growth, while others either have a declining growth rate or, after an initial resting phase, an exponentially increasing volume (Ebara et al., 1986; Okazaki et al., 1989). Clinical prognosis is reliably defined by combining tumor size with liver function and patient's quality of life. For patients with either compensated cirrhosis and a single small HCC (<5 cm) or multinodular tumors, prolonged survival greater than 25% at three years may occur. Survival is approximately 50% for patients with no constitutional symptoms, vascular invasion of the tumor, or extrahepatic spread and with high clinical performance status (Llovet et al., 1999a). Tumor progression and liver failure are the leading causes of death in patients with compensated cirrhosis who were prospectively followed-up (Ganne-Carrié et al., 1996; Llovet et al., 1999a).

4. Treatment

Treatment options have largely been selected according to empirical criteria, such as the presence or absence of cirrhosis, number and size of tumors, and degree of hepatic deterioration (Colombo, 1999). In general, the reassessment of treatment outcomes on the basis of intention-to-treat analysis yielded less encouraging figures (Llovet et al., 1999b).

4.1. Patients with surrounding normal liver tissue

Hepatic resection is the primary option for the few patients with a HCC arising in a normal liver and with well preserved hepatic function. Despite the advanced stage of disease, the five-year survival is approximately 50%. Five-year survival is much less encouraging 20% for patients who undergo orthotopic liver transplantation (OLT) because they did not qualify for simple resection. According to the European Transplantation Registry of OLT, 446 patients with HCC without cirrhosis underwent OLT between 1988 and 1994 and had a 36% five-year survival.

4.2. Cirrhotic patients with small tumor

OLT is the best treatment modality for patients with a solitary <5 cm in diameter HCC or patients with less than three tumors each <3 cm (Milan Criteria) and less than 60–65 years of age (Mazzaferro et al., 1996). The five-year survival of patients fulfilling the Milan criteria is approximately 75% (Mazzaferro et al., 1996; Llovet et al., 1999b; Jonas et al., 2001). The time-lag between candidacy and transplantation introduces a variable that is related to survival. If the waiting period exceeds 6–10 months, the increase in life expectancy provided by OLT is negated by the risks that patients face while waiting for transplantation (Sarasin et al., 1998). On an "intention-to-treat" basis, the proper selection of candidates for resection resulted in a better outcome than OLT (Llovet et al., 1999b). Specifically, the five-year survival after resection of the best candidates i.e. normal bilirubin and mild portal hypertension was 74% compared to a 54% two-year survival after OLT (Llovet et al., 1999b). Thus, cirrhotic patients without clinically relevant portal hypertension and a normal bilirubin should first be considered for resection whereas those with; poor outcome markers should be selected for OLT or if contraindicated, for percutaneous interstitial therapy. The lack of availability of donors excludes of 25–50% of the donor-listed candidates (Schwartz et al., 1997; Llovet et al., 1999b). "Bridge therapies," while awaiting OLT, include locoregional ablative treatment or chemoembolization; both may improve the outcome of OLT (Majno et al., 1997).

Segmentectomy and subsegmentectomy are the best therapeutic options for patients with single small tumors, well preserved hepatic function, bilirubin values below 1 mg/dl and absence of severe portal hypertension (<10 mmHg). The five-year survival in well-selected patients with a

single HCC smaller than 5 cm was 70% (Llovet et al., 1999b).

Survival of patients undergoing hepatic resection is limited by tumor recurrence, its size and invasiveness as well as the functional status of the liver (Child-Pugh score). The three year cumulative survival is approximately 50% for patients with a small tumor and compensated cirrhosis compared to 12% for Child-Pugh B-C patients (Franco et al., 1990).

Patients fulfilling the Milan criteria for OLT but were judged not suitable for OLT or resection can be offered to ultrasound guided interstitial treatments. These approaches include tumor injection with absolute ethanol (PEI), 50% acetic acid or hot saline, or tumor thermoablation with radio frequency, microwaves or laser. As predicted, survival is largely influenced by liver function, size and number of tumors. In an uncontrolled study the five-year survival of PEI treated patients with well-compensated cirrhosis (Child A) and a less than 5 cm tumor was 47 and 29% for those with more advanced liver impairment (Child-Pugh B). Severe complications of these interventions are 1.7% with an associated mortality of 0.1% (Livraghi et al., 1995). Tumor recurs in virtually all treated patients, more often in those with high levels of serum AFP and those without a peritumoral capsule. In prospective randomized studies of patients with compensated cirrhosis and a small HCC, radiofrequency was similar to PEI in terms of complete tumor necrosis but it required fewer treatments (Livraghi et al., 1999; Cioni et al., 2000; Ikeda et al., 2001). Needle-track seeding of tumor cells may be a risk for patients with subcapsular and poorly differentiated tumors (Llovet et al., 2001). Transcatheter arterial chemo-embolization (TACE) of HCC can be offered to patients not suitable for radical therapies but who have preserved liver function (Children A and B) and no vascular invasion of the tumor. TACE administration through the femoral artery leads to ischemic necrosis of the tumor and makes hepatic arterial injection of antitumor agents possible, providing higher local concentrations of drugs with fewer systemic side effects. Three randomised controlled studies of TACE and one randomised controlled study of transarterial embolization (TAE, without chemotherapy) treatment of patients with unresectable HCC (Pelletier et al., 1990, 1998; Groupe d'Etude et de Traitment du Carcinome Hépatocellulaire, 1995; Bruix et al., 1998) failed to show improved survival, indicating that these approaches are not therapeutic options for cirrhotic patients with a multifocal or large HCC. Conversely, two controlled studies showed short-term increased survival (Lo et al., 2002; Llovet et al., 2002).

Systemic chemotherapy is not effective in inoperable HCC, probably due to over-expression of multidrug resistance genes. In the only randomized controlled trial (Lai et al., 1988), doxorubicin not only failed to prolong survival but it also caused fatal complications due to cardiotoxicity. The presence of tumor hormone receptors suggests a potential for hormonal manipulation of tumor growth, particularly using anti-estrogens. However, in a large randomized controlled study of Spanish patients with inoperable HCC (Castells et al., 1995), treatment with the anti-estrogen Tamoxifen did not improve survival or the quality of life, as compared to placebo.

Gene therapy may offer new hopes to many patients with currently untreatable HCC. Tumor cells may be transfected with viruses that can transfer genes to facilitate cell suicide or to make cells more responsive to antiviral drugs (Kanai et al., 1996).

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