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TOPIC HIGHLIGHT

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Hepatocellular carcinoma in patients with hepatitis C virus-related chronic liver disease

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Abstract

Hepatitis C virus (HCV) is a major cause of hepatocellular carcinoma (HCC) worldwide due to the high prevalence of HCV infection and the high rate of HCC occurrence in patients with HCV cirrhosis. A striking increase in HCC incidence has been observed during the past decades in most industrialized countries, partly related to the growing number of patients infected by HCV. HCC is currently the main cause of death in patients with HCV-related cirrhosis, a fact that justifies screening as far as curative treatments apply only in patients with small tumors. As a whole, treatment options are similar in patients with cirrhosis whatever the cause. Chemoprevention could be also helpful in the near future. It is strongly suggested that antiviral treatment of HCV infection could prevent HCC occurrence, even in cirrhotic patients, mainly when a sustained virological response is obtained.

Key words: Hepatocellular carcinoma; Cirrhosis; Hepatitis C virus ; Epidemiology; Screening; Treatment; Prevention

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, with more than 600 000 new cases yearly. Most patients with HCC have an underlying chronic liver disease (often cirrhosis), resulting mainly from chronic infection by hepatitis B virus (HBV), hepatitis C virus (HCV), excessive alcohol consumption, and often an association of these causes. HCC has recently gained more interest due to its increasing incidence in industrialized countries[1,2].

A link between non-A non-B hepatitis and HCC occurrence was firstly suspected in Japan more than 20 years ago due to contrast between simultaneous increase in HCC incidence and decline of HBV infection in this country[1]. This relationship was rapidly confirmed in the early 1990s when specific serum testing for HCV infection became available. HCV was subsequently classified as a human carcinogen in 1994[1]. Almost all cases of HCV-related HCC occur in patients with cirrhosis, which is a well-established precancerous state[3]. However a direct carcinogenetic role of HCV is strongly suspected in humans and supported by experimental models showing the oncogenic effect of viral core and NS3 proteins[4,5].

In this review, we will discuss different aspects of HCV-related carcinogenesis and HCC treatment, focusing on similarities and differences with tumors related to other causes of chronic liver diseases, particularly HBV and alcohol.

EPIDEMIOLOGY

HCV is a major cause of HCC worldwide due to high prevalence of chronic infection affecting about 170 millions of people. In industrialized countries, HCV infection and excessive alcohol consumption are the two leading causes of cirrhosis and HCC is often associated[1,2]. However regional differences have been shown. In Japan, HCV is currently the main cause of HCC accounting for more than 70% of cases. A similar rate is observed in Southern Europe such as Italy or Spain, even if some studies have reported a higher role of alcohol consumption[6]. By contrast, in other countries such as France[7] or Belgium[8], excessive alcohol intake remains the leading cause of cirrhosis and HCC (accounting for more than 60% of cases), HCV being only the second cause (about 25%-30% of cases).

A striking increase in HCC incidence has been observed for more than 20 years in most industrialized countries. This fact has been clearly established from epidemiological

surveillance databases in Japan[9], UK[10], Italy[11], France[12] and the USA[13]. In France, the age-standardised mortality rates per 100 000 people (which reflects incidence due to short life expectancy of patients) due to primary liver cancer (mostly HCC) has increased from 3.2 to 11.1 in men and from 1.2 to 2.5 in women between 1979 and 1994[12]. It is generally admitted that this increase is related to the growing number of patients contaminated by HCV several decades ago who reached the stage of cirrhosis and consequently developed cancer[1,2]. Epidemiological models suggest that this trend would likely persist 10-15 years without strong improvement in treatment efficacy[14]. However additional factors may also contribute to increase HCC incidence such as improved management or prevention of other lethal complications of cirrhosis, oesophageal haemorrhage[15] and bacterial infections resulting in longer survival of patients at high risk. Additionally prevalence of overweight and diabetes type 2 is increasing in developed countries, a factor that favors HCC occurrence[13].

The situation in industrialized countries is in contrast with developing areas such as Eastern Asia and sub-Saharan Africa. In these regions, HBV infection (often associated with aflatoxin exposure) is still the leading cause of chronic liver disease and HCC, accounting for more than 80% of cases[1,2]. The incidence of HCC is notably higher than in industrialized countries and seems to be stable or decreasing, likely due to better control of aflatoxin exposure or HBV infection[9]. However, even in these regions HCV infection has a significant prevalence and is also an important cause of HCC[9].

As a whole HCV-related HCC is currently a major public health problem in many countries worldwide, leading to increased financial burden over time[16].

RISK (OR PREDICTIVE) FACTORS

Almost all the patients with HCV-related HCC have cirrhosis at the time of diagnosis[3]. Therefore cirrhosis, which is associated with genetic alterations predisposing to cancer[17], is the main risk factor for HCC occurrence in these patients. Cases of HCC in patients with chronic hepatitis without cirrhosis have been reported but remains very scarce[18]. A similar feature has been found in patients with alcohol-related liver disease but is markedly different in patients chronically infected by HBV, where HCC occurs before cirrhosis in up to 40% of cases[1]. In cohorts of patients with HCV-related cirrhosis, the risk of HCC occurrence over time is high and roughly linear, between 2% and 8% yearly as a whole[19]. A higher rate has been reported in Japan (4%-8%) than in Western countries (2%-4%) suggesting the influence of yet unknown epidemiological factors[19]. Moreover this risk seems to be higher in HCV-related cirrhosis than in alcohol or HBV-related cirrhosis[19].

Obviously the risk of HCC occurrence is not similar among all patients with HCV cirrhosis. Numerous studies have been performed to identify risk factors on an individual basis[19]. Identifying such factors could lead to important progress in terms of clinical management (see Screening) and understanding of hepatocarcinogenesis[20]. Numerous predictive factors have been identified ranging from simple epidemiological parameters such as age or sex[21] to most sophisticated ones identified by molecular biology[22,23]. However most of the studies have assessed simultaneously a limited number of factors (sometimes only one) precluding global interpretation, and have included patients with different causes of liver diseases although risk factors might be different from a cause to another. The more commonly identified predictive factors (most of them not specific to HCV patients) are age higher than 50, male sex, advanced cirrhosis (reflected by low platelet count or oesophageal varices), high basal alpha-fetoprotein (AFP) serum levels[21,24,25], and more recently overweight and diabetes[26,27]. Factors can be combined in scores or indexes allowing to split patients between different categories of HCC risk. In a recent Japanese study performed in 183 patients with HCV cirrhosis, the estimated risk of HCC at 5-year ranged between 9% and 64% according to the value of a score combining age, sex, serum AFP and platelet count[21]. The influence of tobacco smoking or HCV genotype remains controversial[19]. Histological lesions such as large cell dysplasia[25] and regenerative and proliferative changes[28] have been also reported to increase the risk of cancer, but their assessment requires liver biopsy interpreted by an experienced observer and therefore their practical relevance is less important. Iron overload does not seem to influence carcinogenesis in HCV patients conversely to alcoholics[29]. The association of other causes of liver diseases, such as concomitant HBV infection or high alcohol intake, markedly enhances the risk of HCC in patients with HCV cirrhosis. A potential role of occult HBV infection in HCV-related HCC has also been suspected[30].

NATURAL HISTORY

The characteristics of patients at the time of HCC diagnosis are influenced by the aetiology and the status of the underlying liver disease. They may influence prognosis and the choice of treatments. Patients with HCV-related HCC are usually older than those with alcoholic or HBV-related cirrhosis, a difference likely due to the age at exposition to causative agents (childhood for HBV, adulthood for HCV) or in the rate of progression to cirrhosis (faster for alcoholics)[11,31,32]. The sex ratio is close to one, in contrast with the high prevalence of males in patients with HCC due to alcohol[6]. Tumors seem to be more often unique and small-sized (that is to say slow growing) in patients with HCV cirrhosis in comparison with HBV, even if this fact remains controversial[6]. Liver function is usually more preserved in patients with viral cirrhosis than in those with alcoholic cirrhosis[6]. However whether those differences are related to the natural history of the disease or to the management of patients or both is not determined. As an example compliance to HCC screening (see below) is markedly lower in patients with alcoholic cirrhosis[8].

As a whole survival remains low in patients with HCC (median < 6-12 mo), reflecting the currently high number of advanced tumors at diagnosis and the subsequent

poor efficacy of treatment. However marked differences are observed among etiological groups and individual patients. The characteristics of cancer as well as of the underlying liver disease influence survival as reflected by parameters relevant in prognostic classifications[33]. HCC is clearly the main cause of death in patients with HCV-related cirrhosis[34,35]. In a recent Italian prospective study including 214 patients[34], HCC developed in 32%, ascites in 23%, jaundice in 17%, upper gastrointestinal bleeding in 6%, and encephalopathy in 1% during a follow-up of 17 years. This outcome differs markedly from patients with alcohol-related cirrhosis, the complications of liver failure and portal hypertension being still the leading cause of death[36], a difference that could be in part explained by compliance of patients to clinical management. For instance, the rates of endoscopic screening of oesophageal varices and preventive measures for haemorrhage or bacterial infection is not clearly stated in most published studies[37].

TREATMENT

In patients with HCC, treatment decision depends on several factors including size and extension of tumor, liver function, and general condition of the patient (such as age, comorbidities and general status)[38,39]. There is currently no medically validated therapy, even if recent characterisation of molecular pathways of hepatocarcinogenesis raises some hope for the future[23]. Intra-arterial chemoembolization has been claimed to result in survival improvement in selected cases but contra-indications, mainly due to liver failure, are frequent and the number of eligible patients who would really benefit from it is low[40,41]. Despite these reservations, patients with underlying viral disease seem to have a more favourable outcome and a lesser rate of post-procedure complications than patients with alcoholic cirrhosis.

Important advances have occurred concerning curative treatment of small tumors, even if randomized trials are lacking to definitely establish their benefit[39]. Milan criteria, defined as either one nodule less than 5 cm in diameter or 2 or 3 nodules each less than 3 cm in diameter, help select patients eligible for transplantation but increasingly also for other curative options[42]. Liver transplantation, which is the best curative option for the long term as it is able to remove the tumor and the underlying cirrhosis (preventing therefore the occurrence of new tumors), can be performed in only limited number of well-selected patients[42]. Other curative options, resection and percutaneous ablation mostly by radiofrequency, are able to cure the tumor mostly when small and well circumscribed[43]. Due to a lesser mortality and morbidity and a less deleterious influence on liver function, radiofrequency is to be performed in an increasingly larger number of patients with cirrhosis as new techniques allow now to treat tumors more than 3 cm in diameter. Nevertheless tumor recurrence rate is high (10%-20% per year) in cases of resection or radiofrequency due to either intrahepatic metastasis or occurrence of a new HCC, a case that is particularly frequent in patients with HCV infection. This fact justifies post-therapeutic surveillance of patients and the search for preventive treatments[42] (see Prevention).

The choice of therapy in patients with HCC is largely independent of the aetiology of the disease. However, as previously stated, patients with HCV-related HCC have a better liver function than alcoholic patients. Therefore they are less prone to develop liver failure after aggressive procedures. This fact might explain the better results of arterial chemoembolization in patients with viral disease compared with patients with alcoholic cirrhosis[41]. This might also partially explain the lesser mortality and morbidity of patients after hepatectomy in Asian countries in contrast with Western and their better overall outcome[42]. Conversely it has also been suggested that hepatic recurrences after surgery or ablative therapy are more frequent in patients with HCV-related HCC, possibly due to a higher incidence of new tumors, but this point needs confirmation[44].

SCREENING

The failure to improve survival in patients with advanced HCC has led to the development of screening strategies aiming to detect small tumors treatable by curative methods. Screening is currently based on regular periodic ultrasonography (US) in patients with cirrhosis[2]. A focal lesion discovered by screening indicates recall procedures, mainly imaging methods with vascular injection of contrast media (TDM, MRI, US)[45] and (in restricted cases) liver biopsy. This is especially important in case of a nodule below 1-2 cm in diameter because as it might be a non cancerous macronodule (which may remain stable or even disappear spontaneously over time) in more than fifty percent of cases[46]. Cholangiocarcinomas and liver lymphomas may also occur in patients with HCV cirrhosis, even if rare[46]. A diagnostic algorithm based on focal lesion size has been proposed by the international Barcelona conference in 2000[38] and recently modified[39]. The usefulness of serum AFP or other serum markers for screening is doubtful[2] due to high rates of false negatives (serum AFP is rarely increased in patients with small HCC) and false positive results, particularly in HCV cirrhosis[47]. The periodicity of screening is not established, an interval of 6 mo being usually recommended[39].

HCC screening is now recommended for every patient with cirrhosis, whatever the aetiology (and also for some patients with HBV infection without cirrhosis)[48]. However, as previously stated, HCC occurrence is strongly influenced by the cause of liver disease and numerous individual risk factors[19]. It is likely that non selective screening may lead to unjustified medical burden and costs. Therefore there is an urgent need to predictive scores using parameters recordable at bedside[21,27] and to validate them in prospective studies performed in well-defined populations, particularly according to the aetiology of cirrhosis. If HCV patients with bridging fibrosis at biopsy (stage F3 in Metavir classification) are candidates; screening is still debatable, even if sometimes recommended.

Even if a survival benefit has not been established (randomized trials being ethically questionable), HCC screening is now largely performed in industrialized

countries[49,50], leading to a better knowledge of liver carcinogenesis and an increasing rate of small HCC at diagnosis[51].

PREVENTION

The goal of primary prevention is to avoid or delay the occurrence of HCC by using medical treatments[52,53]. Chemoprevention is obviously a complementary method to screening to improve survival. At present there is a growing set of data suggesting the preventive role of antiviral drugs in patients with HCV-related chronic liver disease[52,53], alfa interferon being the most extensively studied drug. In patients with chronic hepatitis and only mild fibrosis, a virtual eradication of long term risk of HCC (and other complications) is associated to sustained virological response. However this effect remains debated in patients with established cirrhosis, mainly because most studies were retrospective and non randomized, and subjected to bias. Only two small randomized trials have been published with conflicting results[54,55]. Two metaanalyses[56,57] have suggested a moderate preventive effect on HCC occurrence in patients treated by alfa interferon by comparison to untreated patients. This effect was largely independent of virological response. However the studies included in those metaanalyses have been performed using monotherapy by standard alfa interferon with very low rates of sustained virological response. Some recent studies including larger cohorts of patients[58] treated by bitherapy[59] suggest a higher preventive effect, particularly in patients with sustained virological response. Those results are to be confirmed but encourage treating patients with compensated cirrhosis. The efficacy of long term low doses of pegylated interferon need to be established by ongoing randomized trials that could also identify predictive factors of a favourable result[52,53].

Another concern is the extremely high rate of recurrences following local curative treatment either by resection or percutaneous ablation of a first HCC. Secondary prevention should be aimed at decreasing either local recurrences (corresponding to treatment failure) and/or distant recurrences (corresponding to metastasis or to new HCC)[52,53]. Randomized trials performed in patients with cirrhosis mostly due to HCV infection have suggested a benefit in recurrence rate and survival using polyprenoic acid (a non commercialized retinoid derivative), adoptive immunotherapy, continuous or intermittent interferons alfa and beta treatments, and intraarterial radioactive iodine injection mixed with lipiodol[52,53]. These studies need confirmation because of their small sample size and have not lead up to now to important practical progress. Similarly to primary chemoprevention, post-procedure antiviral treatment using pegylated interferon alone or pegylated interferon and ribavirin might reduce recurrences if sustained viral response is obtained. Well-designed (randomized) trials involving large numbers of patients are still needed.

CONCLUSION

Some major questions should be addressed in the near future, particularly (but not only) in patients with HCV cirrhosis. It is still difficult to identify patients with compensated cirrhosis who require specific management including HCC screening and chemoprevention. Many of them are asymptomatic and undiagnosed. Even in patients suspected of having cirrhosis, a reliable confirmation requires liver biopsy, an ill-accepted and costly procedure. Non invasive methods of assessment of liver fibrosis, such as elastometry (Fibroscan®, Echosens, Paris, France)[60] or blood tests[61,62], might facilitate early diagnosis of cirrhosis, particularly in HCV infected patients. Future prospective studies concerning risk factors of HCC and predictive scores should take into account the periodic evaluation of those parameters. Thirdly the preventive effect of antiviral treatment in patients with HCV cirrhosis, including new molecules in development[63], should be precisely assessed in prospective trials.

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