Hepatitis B virus-related hepatocellular carcinoma: primary, secondary, and tertiary prevention

Anna Giacomin[a], Nora Cazzagon[b], Adriana Sergio[a], Veronica Vanin[a] and Fabio Farinati[a]

With respect to hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC), primary, secondary, and tertiary prevention measures have been or should be adopted. In primary prevention, behavioral patterns represent an important risk factor for HBV infection and should be controlled, discouraging those favoring infection. Interferon treatment shows a modest effect in reducing HCC risk in treated patients, but the data obtained cannot be converted in clinical practice. Nucleoside analogs significantly reduce, but do not abolish, HCC risk in patients with cirrhosis, and should therefore be used in patients with cirrhosis and also to diminish the risk of the other potential complications. With respect to secondary prevention, surveillance with semiannual ultrasound examination is indicated in patients with HBV-related cirrhosis as well as in other subgroups of patients, depending on racial and geographical pattern. Finally, the role of interferon in tertiary prevention of HCC relapse after radical treatment is still under debate; some evidence in favor of the treatment is present, but side effects due to toxicity are frequent and severe enough to limit patients' compliance substantially. As there is definitely no agreement on the efficacy and cost-effectiveness of antiviral treatment in HCC prevention, there is still a need for well-constructed, large size, and randomized prospective trials to confirm what is still required based on expert opinion rather than on sound scientific evidence.

European Journal of Cancer Prevention 2011, **20**:381–388

Keywords: antiviral therapy, hepatitis B virus infection, hepatocellular carcinoma, nucleos(t)ide analogs, pegylated interferon, prevention, vaccination

[a]Department of Surgical and Gastroenterological Sciences, Section of Gastroenterology, University of Padova and [b]Venetian Oncology Institute, I.R.C.C.S., Padova, Italy

Correspondence to Fabio Farinati, MD, PhD, Department of Surgical and Gastroenterological Sciences, Section of Gastroenterology, University of Padova, Via Giustiniani 2, Padova, Italy
Tel: +39 049 8211305; fax: +39 049 8212887;
e-mail: fabio.farinati@unipd.it

Received 3 December 2010 **Accepted** 28 February 2011

Introduction

Hepatitis B virus (HBV) infection represents one of the main causes of liver cirrhosis and hepatocellular carcinoma (HCC) worldwide, particularly in Asia and sub-Saharan Africa. Global estimates indicate that approximately one-third of the world population (two billion people) has been infected by HBV and more than 350 000 million (6% of the world population) are chronic carriers. After acute infection, up to 10% of adults and 30–90% of infants develop chronic hepatitis, a condition that may lead to liver cirrhosis and HCC (with a relative risk with respect to the uninfected population ranging from 5 to 96%). HBV-related HCCs account for 15% in developed countries and 80–90% in Africa and Asia, where HBV infection is endemic and characterized by a high rate of vertical transmission. Overall, on worldwide basis, HBV is the etiologic attributable factor in more than 50% of the cases of HCC (Perz *et al.*, 2006). In Italy, HBV-related HCC accounts for approximately 10% of the cases (the more accurate estimates indicate a share in 12% of the cases), with negligible variability over time up to 2008, and the cumulative probability of HCC at 5 years in HBV-related cirrhosis ranges between 9 and 25%. Coinfection with hepatitis C virus (HCV) or hepatitis delta virus almost doubles the risk (Chiaramonte *et al.*, 1999; Benvegnù and Alberti, 2001; Stroffolini *et al.*, 2005; Romeo *et al.*, 2009).

HBV-related liver damage represents an ideal scenario for HCC prevention; measures could be adopted to avoid the infection, stop the evolution of chronic liver damage, and interfere with the carcinogenesis process (primary prevention), reach an early diagnosis of the disease (secondary prevention), and even to reduce the risk of HCC recurrence after primary treatment (tertiary prevention). This study is devoted to describing the overall scenario of prevention of HBV-related HCC, and to identify the most feasible and efficient options.

Primary prevention

Behavioral patterns

Even though the risk of HBV infection becoming chronic and eventually leading to HCC is higher for vertical transmission, there are obvious considerations to be taken with respect to avoiding the spread of HBV infection through risky behavioral patterns such as unprotected sexual intercourse or beauty treatments like tattooing and body piercing. These beauty treatments are definitely

0959-8278 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CEJ.0b013e328346399b

increasing in popularity, and as they are definitely associated with an increased risk of hepatitis virus infection spreading (Mariano *et al.*, 2004), it may be expected that the proportion of cases of parenterally transmitted hepatitis due to such exposure will increase in the years to come. Therefore, specific efforts are required to implement controls for the use of disposable materials and for effective sterilization of instruments used during beauty treatments, which should be also discouraged in teenagers by targeted information campaigns. The same is true with respect to risky sexual behaviors and, in particular, to sexual tourism, which is ethically detestable and represents one of the most frequently documented risk factors for travel-related hepatitis B (Keystone, 2005).

Vaccination

The first approach to HBV-related diseases and cancer prevention is to limit the spread of viral infection in primary prevention by the most powerful and cost-effective method, that is, vaccination.

The earlier plasma-derived vaccines were developed in the 1980s; in the 1990s second and third generation vaccines, recombinant and more immunogenic, were created to offer a higher degree of protection even in immune-compromised patients and in nonresponders.

The most important issue for public health was represented by the selection of the target population. In the beginning, vaccination was offered only to at-risk groups such as homosexuals, drug abusers, health care workers, patients undergoing frequent transfusions or hemodialysis, newborns of HBsAg-positive women, household contacts of chronically infected patients. This strategy, still adopted in some low-incidence developed countries, was only partially effective. The modest results obtained in reducing the burden of HBV-related diseases might have been due to people migration, difficulty in effectively reaching at-risk groups, as well as by HBV prevalence and transmission in risk-free populations (30% of HBsAg-positive patients have no risk factors in their history). For this reason, besides widening the target of vaccination campaigns offered to high-risk groups and implementing public health campaigns, in 1991 the World Health Organization recommended universal vaccination to be introduced with the routine immunization of newborns, infants, or adolescents. By 2006, 168 countries had already started a program of universal vaccination, with an infant coverage of more than 80% in 131 of 168 countries (Zanetti *et al.*, 2008; Beasley, 2009).

The initial results were shown in the changes of the incidence and prevalence of HBV infection. In high prevalence countries that first introduced vaccination (Taiwan, Thailand, Namibia, and Gambia), the results were outstanding. In Taiwan, where universal vaccination was started in 1984, the HBcAb carrier rate among children fell from 26 (1984) to 4% (1994); HBsAg carriers decreased as well from 9.8 to 1.3%. Average mortality for fulminant hepatitis showed a significant reduction from 5.36 of 100 000 to 1.71 of 100 000. The same trends were observed in other countries as well (Viviani *et al.*, 1999; Lee *et al.*, 2003; Chan *et al.*, 2004; Wichajarn *et al.*, 2008). In Gambia, a reduction in childhood HBsAg prevalence from 10 to 0.6% was obtained; whereas in Malaysia, among children aged 7–12 years, a drop from 1.6 to 0.3% was observed.

A more recent serological survey was conducted in China in 2006, and the results were compared with those of 1992. It showed that, after universal vaccine introduction (and principally after the introduction of free of charge vaccination of newborns in 2005), both HBsAg and anti-HBc prevalence decreased in vaccinated cohorts in comparison to unvaccinated (2.1 vs. 9.4% and 8.5 vs. 41.1%, respectively). Remarkably, among children younger than 5 years, born after the routine childhood immunization recommendation, the prevalence was only 1.0%, with a 90% reduction. Despite being more impressive in younger age classes, initial effects were seen even in the larger population aged 1–59 years, with HBsAg prevalence decreasing from 9.8 to 7.2% (Liang *et al.*, 2009).

A corresponding decrease in HCC incidence and mortality was shown in the Taiwanese pediatric population (where primary liver cancer is sufficiently frequent to be studied). In the decade of 1984–1994, HCC incidence fell from 0.7 to 0.36% and related mortality from 0.8 to 0.3% (Chang *et al.*, 1997); the same was described in Thailand (Wichajarn *et al.*, 2008).

Good results, even if less impressive, as the incidence of HBV infection and of HBV-related HCC in children is lower, were reported in intermediate prevalence countries, like Malaysia (Bhimma *et al.*, 2003) and Italy (Bonanni *et al.*, 2003). Our vaccination program started in 1991; after 10 years acute hepatitis incidence had fallen from 11 to 1.6 of 100 000 for infants and from 17 to 0.5 for adolescents. No data are available yet on HCC, but we can imagine a further shrinkage in the percentage of HBV-related liver cancer, which could however be tempered by the arrival of immigrants to Italy from medium to high risk countries (Fabris *et al.*, 2008; Majori *et al.*, 2008; Coppola *et al.*, 2010; Tafuri *et al.*, 2010).

In low prevalence countries the trend is similar, but the most interesting data are derived from relatively high-risk subgroups. In the United States, overall the incidence of infection in young people dropped from 3 to 0.19 of 100 000; and in Alaska, where the infection rate in children was 10% and HCC had an average prevalence of 1.9 of 100 000, after the vaccination era the figures became 1.5% and about 0, respectively. The same happened in Georgia, a country that had registered an incidence of HBV higher than other nations due to the high number of Asiatic immigrants.

Cost-effectiveness analysis (Hung and Chen, 2009; Plymoth *et al.*, 2009) confirm both the efficacy of universal vaccination in reducing long-term sequelae of acute hepatitis B infection (by more than 80%) and its cost-effectiveness, by means of reducing HCC death and chronic illnesses.

Treatment of chronic HBV-related liver diseases

Interferon

Studies on the natural history of chronic HBV infection have shown that active HBV replication contributes to the development of acute hepatitis flare, hepatic decompensation, cirrhosis, and HCC. Theoretically, cessation of HBV replication may reduce the risk of complications and improve prognosis (Chu, 2000). This aspect has been supported by two large studies: in the former, a prospective cohort study with 11 years of follow-up, Chen *et al.* (2006) observed that there was a significant increase in HCC-related mortality across viral load categories, with a relative risk for HCC mortality in the low viral load group of 1.7 (95% CI: 0.5–5.7) compared with 11.2 (3.6–35.0) in the high viral load group. In the latter (the REVEAL study), a direct correlation between baseline HBV-DNA levels and the incidence of HCC was shown (Chen *et al.*, 2009) and elevated serum HBV-DNA levels ($>10\,000$ copies/ml) were identified as a strong predictor of HCC evolution, independently of HBe status, serum alanine aminotransferase level, and presence or absence of liver cirrhosis. HBeAb-positivity is believed to correlate with a lower viral load and to indicate a favorable outcome and a lower risk of HCC development (Fattovich *et al.*, 1986; Di Marco *et al.*, 1999), whereas, in contrast, an increased risk of HCC is associated with HBeAg-positivity (Yang *et al.*, 2002). These results suggested that a continuous antiviral therapy, aimed to suppress viral load, may reduce the risk of complications from HBV infection, including tumor development, and the rate of disease progression (Lok, 2004).

Interferon (IFN), beyond its activity in reducing viral load, has other additional mechanisms of activity that could be of interest in reducing cancer risk. It downregulates tumor growth, induces over-expression of adhesion molecules, boosts NK lymphocyte activity, increases spontaneous cytotoxicity, has antiangiogenetic activity, blocks the Jack/Stats pathway, and induces upregulation of the HLA-MHC1 system in tumor cells (Jonasch and Haluska, 2001; Gresser, 2007).

IFN-α has been used in the treatment of chronic hepatitis B for decades and beneficial effects including HBeAg/HBV-DNA seroclearance, reduction of HCC development, and better complication-free survival have been documented. However, the effect on the prevention of cirrhosis and HCC development was controversial, particularly in earlier studies. In Yuen's experience, no long-term benefit was shown (Yuen *et al.*, 2001) and Bonino, in his study on HCV-related hepatitis, did not observe any protective effect of IFN in antiHBc-positive patients (Bonino *et al.*, 1997). On the other hand, Lin *et al.* (1999) and Ikeda *et al.* (1998) described a significant reduction of HCC incidence after IFN treatment. The major reasons for the inconsistency of the data are the relatively small sample size included in the studies, the low response rate, the lack of adequate controls, the short follow-up period, and different patient age at enrollment.

Later studies were aimed at clarifying the matter. In a study by Lin *et al.* (2007), the long term outcome in 233 INF-treated patients was compared with that observed in a 1 : 1 well-matched untreated control population. The cumulative incidence of cirrhosis at the end of 15 years of follow-up (median 6.8 years; range, 1.1–16.5 years) was 17.8% in the IFN-treated patients versus 33.7% ($P = 0.041$) in those untreated. The incidence of HCC was significantly higher in the control group than in the IFN group ($P = 0.011$), and was highest in nonseroconverters of the control group. This finding was also confirmed when only patients with preexisting cirrhosis were considered (58.9 vs. 19.7%, $P = 0.0086$), but not in patients without preexisting cirrhosis (2.3 vs. 2.1%), thus showing that the more advanced the disease, the higher is the chance of modifying the disease natural history. On multivariate analysis, IFN therapy ($P = 0.027$) was identified as an independent protective factor against the development of HCC.

In the last few years several meta-analysis were carried out to overcome the problem of the variability in the results obtained in the studies and to confirm or deny the role of IFN in HCC prevention.

Cammà *et al.* (2001) in their meta-analysis identified three randomized controlled trials and 15 nonrandomized controlled trials comparing IFN-treated and untreated patients with cirrhosis. First of all, a remarkable heterogeneity was detected among studies, with variable IFN schedules being used, both with respect to the total dose and the length of treatment.

The rate of HCC in treated and untreated patients with HBV-related cirrhosis was reported in seven studies, including 1505 patients with 122 observed HCC cases. The administration of IFN decreased the rate of HCC development in all trials, but a significant difference was observed in only three studies. The pooled estimate of the preventive effect of treatment was in favor of IFN ($P < 0.001$). As the seven studies showed inconsistency, subgroup analyses were carried out in relation to the ethnic origin of patients (European vs. Oriental studies). Consistent results were observed only when assessing data pooled from European reports in which no preventive effect for HCC was shown. Cammà *et al.* (2001) concluded that IFN prevents or delays the development of HCC in patients with HCV-related cirrhosis (also investigated in the meta-analysis), whereas in HBV-related cirrhosis it does not.

In the meta-analysis published by Sung *et al.* (2008), 12 studies enrolling patients treated with IFN versus control, and five studies enrolling patients treated with nucleoside analogs, were selected. The analysis showed that the risk of HCC after IFN treatment was reduced by 34% but it is noteworthy that nucleoside analogs treatment showed a more profound reduction in HCC, reaching 78%. However, these results have to be cautiously interpreted given that only five studies were available in the literature using antiviral agents. Again, beneficial effects were more significant among patients with early cirrhosis than among those without cirrhosis. None of these studies assessed HCC development in relation to HBeAg status after treatment (i.e., number of HCC cases with or without HBeAg seroconversion). This meta-analysis has many limitations: small number of randomized controlled trials and suboptimal quality, and no studies in which pegylated IFN was used.

An additional meta-analysis was published by Yang *et al.* (2009). The author selected 12 controlled trials, including 2082 patients, comparing IFN with no treatment, and concluded that IFN prevents or delays the development of liver cirrhosis and HCC over the long-term in patients with chronic hepatitis B. Their results were somewhat different from the meta-analysis published in 2001 by Cammà *et al.*, the results of which showed that when assessing data from five European reports, the overall preventive effects of IFN were not significant. But the five studies were relatively small and included only 412 patients in total, 189 patients in the IFN–treated group and 253 patients in the untreated group. In Yang's meta-analysis, 2082 patients from many different regions, not limited to Europe, were included and an amplified preventive effect of IFN was observed, thus confirming the benefit exerted by IFN treatment on the prevention of liver cirrhosis and HCC.

To sum up, these studies suggest a potential benefit of treatment in reducing the risk of HCC development, but the data are still not sound enough to change the current guidelines.

Nucleos(t)ides analogs

As far as nucleos(t)ide analogs are concerned, their role in preventing HCC has been thoroughly investigated but the largest number of studies available considered only lamivudine, as it was the first antiviral agent chronically administered to reduce viral load in patients with chronic HBV-related liver disease.

In 2004, Liaw *et al.* (2004) presented the results of the CALM study (for the Cirrhosis Asian Lamivudine Multicentre Study Group), a large randomized controlled trial, in which 651 patients with chronic hepatitis B, who had histologically confirmed cirrhosis or advanced fibrosis, were randomly assigned in a 2 : 1 ratio to receive lamivudine (100 mg per day; 436 patients) or placebo (215 patients) for a maximum of 5 years. This study led to two important conclusions about continuous lamivudine treatment: (i) this strategy delayed clinical progression in patients with chronic hepatitis B and advanced fibrosis or cirrhosis by significantly reducing the incidence of hepatic decompensation; in fact, the Child-Pugh score increased in 3.4% of the patients receiving lamivudine versus 8.8% of those receiving placebo (hazard ratio 0.45; $P = 0.02$) (ii) it reduced the risk of HCC, which occurred in 3.9% of patients in the lamivudine group and 7.4% of those in the placebo group (hazard ratio 0.49; $P = 0.047$), therefore decreasing but not abolishing HCC risk.

In the same year, in Italy the AISF (Italian Association for the Study of Liver Disease) Lamivudine study analyzed the virological and clinical events observed during lamivudine therapy in patients with HBeAg-negative chronic hepatitis. Patients who had cirrhosis and who maintained virological response were less likely to develop HCC ($P < 0.001$) and disease worsening ($P < 0.001$) than those with viral breakthrough (Di Marco *et al.*, 2004). However, the risk of HCC was again reduced but not abolished.

These data seem to have been recently confirmed by another prospective study in which similar results were obtained. The data were stratified according to the underlying liver status and to the ontreatment viral response during long-term lamivudine therapy in patients with HBV-related liver disease. The cumulative incidence of HCC in patients with sustained viral suppression was significantly lower than in patients with a suboptimal response and in the controls ($P = 0.002$ and 0.005, respectively). A preventive effect of lamivudine on the development of HCC was confirmed in patients with compensated cirrhosis but was not observed in patients without cirrhosis and with decompensated cirrhosis ($P = 0.446$ and 0.123, respectively). Risk assessment for the development of HCC is possible based on the ontreatment viral response during long-term lamivudine therapy in HBV-related liver disease (Eun *et al.*, 2010).

A large Japanese retrospective multicenter study recruited 377 patients who received lamivudine; another 377 were selected as matched untreated controls. In the lamivudine group, HCC occurred in four patients (1.1%) with an incidence rate of 0.4% patients per year, whereas in the control group HCC occurred in 50 patients (13.3%) with an incidence rate of 2.5% per year. A comparison of the cumulative HCC incidence between the two groups by the Kaplan–Meier method showed a significantly lower incidence of HCC in the lamivudine group ($P < 0.001$; Matsumoto *et al.*, 2005). Additional studies confirmed these results in another case–control study, 142 HbeAg-positive patients treated with lamivudine had a lower incidence of HCC and/or cirrhosis with

respect to 124 controls ($P = 0.03$), the YMDD mutations reducing the benefits of the lamivudine therapy (Yuen *et al.*, 2007).

From a recent meta-analysis of the randomized controlled trials, recruiting overall 753 cirrhotic patients, the number of events (HCC development) with nucleoside analogs treatment (all analogs were considered) was 17 of 436 (3.8%) whereas 71 of 317 (22.4%) events were observed without treatment, with a relative risk reduction to 0.17 (95% CI: 0.04–0.79; Sung *et al.*, 2008).

Moreover in the recent Papatheodoridis meta-analyses on 21 studies carried out in chronic hepatitis B patients treated with nucleos(t)ide analogs the following results emerged:

(1) HCC was diagnosed in 2.8 and 6.4% of treated and untreated patients, respectively, during a 46 (32–108) month period ($P = 0.003$);
(2) in 10.8 and 0.5% of nucleos(t)ide naive patients with and without cirrhosis ($P < 0.001$)
(3) in 17.6 and 0% of lamivudine resistant patients with and without cirrhosis ($P < 0.001$).
(4) HCC developed less frequently in nucleos(t)ide naive patients compared with those without virological remission (2.3 vs. 7.5%, $P < 0.001$);
(5) there was no difference between lamivudine-resistant patients with or without virological response to rescue therapy (5.9 vs. 8.8%, $P = 0.466$; Papatheodoridis *et al.*, 2010).

Further data on the new nucleotide analogs are being published. Lampertico *et al.* (2007) analyzed the outcomes of a combination therapy with adefovir (10 mg) in addition to lamivudine (100 mg) in lamivudine-resistant patients. Among 94 HCC-free cirrhotic patients treated, 11 (12%) developed *de novo* HCC after 3–38 months of treatment (median 12 months). In six patients, HCC developed even after serum HBV-DNA clearance, whereas in the other five patients it developed in the presence of persistent viremia, despite adefovir administration. The 4-year cumulative probability of developing HCC was 15%.

The use of adefovir is at the moment considered a second line or an add-on treatment after the development of lamivudine resistance. Hosaka *et al.* (2010) identified aspartate transaminase (AST) levels, the appearance of YIDD mutations, and the presence of cirrhosis as independent predictors of HCC development on multivariate analysis.

Secondary prevention

The need for surveillance of HCC in patients with chronic liver damage, and specifically in cirrhosis, is by now well standardized, following the EASL and AASLD guidelines (Bruix *et al.*, 2001; Bruix and Sherman, 2005). Again according to the AASLD guidelines, in their last updated version (Bruix and Sherman, 2011), HBV-positive patients should undergo surveillance when they develop cirrhosis and also despite not having developed clear-cut cirrhosis, and when they have chronic HBV infection, and are in one of the following conditions:

(1) Asian males over the age of 40 years and females over the age of 50 years;
(2) Patients with family history of HCC;
(3) Africans/North American Blacks.

The surveillance benefit remains uncertain in HBV carriers younger than 40 (when males) or 50 years of age (when females), thus making the calculation of the cost–benefits ratio uncertain. In most studies the role of ultrasound examination in surveillance seems to be well coded (Lencioni, 2010), and the better schedule is every 6 months (Santi *et al.*, 2010), while the debate is still open regarding the need for coupling ultrasound with α-fetoprotein (Farinati *et al.*, 2006; Sherman, 2010). In other studies, however, the optimal screening method and schedule is still uncertain (Cabibbo and Craxí, 2010). Nevertheless, in Italy, HCC was diagnosed during follow-up protocols in 45% of the cases, already in 2002 (Trevisani *et al.*, 2002); in the United States, the figure is much lower (around 17%) even now (Davila *et al.*, 2010). Surveillance is effective in CHILD A cirrhosis but much less in patients with decompensated disease, and in patients with CHILD C cirrhosis it should be carried out only when they have been considered for liver transplantation (Trevisani *et al.*, 2007; Bruix and Sherman, 2011). Patients' age, instead, should not be regarded, to a reasonable limit, as a contraindication to surveillance (Trevisani *et al.*, 2004; Mirici-Cappa *et al.*, 2010). There is only one prospective randomized study showing that surveillance corresponds to a clear gain in survival (Zhang *et al.*, 2004), while most data derive from case–control studies, still the amount of data confirming the impact of surveillance on survival is huge (Bolondi *et al.*, 2001; Trevisani *et al.*, 2004).

Tertiary prevention

High viral loads seem to be strictly correlated to the risk of complications of HBV infection, not only with respect to the primary tumor development and to disease progression (Lok, 2004), but also with late recurrence of HCC after primary treatment.

In Taiwan, 193 patients with HBV-related HCC who underwent tumor resection (193 patients) were prospectively evaluated. During a follow-up period of 58.2 ± 44 months, 134 patients developed HCC recurrence (70%). Multivariate analysis determined that HBV-DNA levels of more than 10^6 copies/ml (2.548, 1.040–6.240 units), together with Ishak hepatic inflammatory activity of more than 6, multinodularity and indocianine green clearance of more than 10%, were significantly associated with late recurrence (more than two years after resection). Nonetheless, patients with high viral loads tended

to have higher Ishak inflammatory ($P = 0.001$) and fibrosis scores ($P = 0.007$) than those with lower loads (Wu *et al.*, 2009).

A second case–control study supported this hypothesis, suggesting that, to prevent long-term recurrences, antiviral therapy should be initiated in patients with detectable serum HBV-DNA. During follow-up, nonviraemic patients had a lower 5-year cumulative recurrence rate (54.7%) than those with persistent viraemia (72.9%; $P = 0.043$). In the multivariate analysis, sustained viraemia ($P = 0.041$) increased recurrence independently (Kim *et al.*, 2008).

A number of randomized controlled trials investigating the effects of IFN on survival and tumor recurrence after curative resection or ablation of HCC were inconclusive, either because effects were not statistically significant or because they were considered only for defined subpopulations (Ikeda *et al.*, 2000; Clavien, 2007).

Recently, a randomized controlled trial on IFN versus control, including 236 patients, after resection was carried out. It showed that IFN treatment delayed recurrence and improved the survival of patients after curative resection of HBV-related HCC, with acceptable toxicity. Recurrence was observed in 67 patients in the IFN treatment group and in 71 patients in the control group. The median disease-free survival in the IFN treatment group was 31.2 (95% CI: 14.8–47.7) months and 17.7 (95% CI: 9.2–26.3) months in the control group, but the difference was not statistically significant. During the first 18 months after resection (the planned duration of IFN-α treatment), the recurrence rate in the control group was significantly higher than that in the IFN-α treatment group [49.2% (58 of 118) vs. 36.4% (43 of 118)], but the significance was lost after 18 months. Multivariate analysis showed that IFN-α treatment ($P = 0.001$), cirrhosis ($P = 0.023$), tumor size ($P = 0.000$), microvascular invasion ($P = 0.002$), and tumor cell differentiation ($P = 0.016$) were independent factors for overall survival (Sun *et al.*, 2006).

Another randomized controlled trial on adjuvant IFN therapy in patients with predominantly HBV-related HCC was published in 2007. The study did not show any significant effect of therapy on the overall recurrence rate in the total patient population. Exploratory subset analysis showed that adjuvant IFN had no survival benefit for pathological Tumor-Node-Metastasis (pTNM) stage I/II tumor but prevented early recurrence and improved the 5-year survival of patients with stage III/IVA tumor (from 24 to 68%, $P = 0.038$; Lo *et al.*, 2007).

Breitenstein *et al.* (2009) carried out a meta-analysis, including all the previous randomized controlled trials, to estimate the effects of IFN on 2-year outcome. This analysis shows that IFN improves outcome after curative treatment of HCC, but severe side effects are common (fever, chills, myalgia, and headache) in all of the studies. A dose reduction of more than 50% because of severe side effects, such as hematological disorders, malaise, hyperthyroidism, hepatotoxicity, and depression, was required in up to 25% of the patients.

Mazzaferro *et al.* (2006) investigated the problem in a prospective randomized study in which patients were substratified into HCV-pure and HCV with antiHBc-positive groups. The study showed a 50% reduction in late recurrences in the treatment arm, but restricted to HCV-pure patients who had been adherent to IFN administration, while the presence of antiHBc antibodies made any difference disappear.

A recent retrospective cohort study (Qu *et al.*, 2010) showed that treatment with IFN-α after tumor resection was associated with a significantly lower cumulative risk of recurrence compared with no treatment. Alpha-fetoprotein (AFP) levels of 400 ng/ml or more, HBV-DNA levels of 4 log10 copies/ml or more, microvascular invasion, and absence of postoperative IFN-α treatment were independent risk factors for HCC recurrence after curative resection.

As for nucleoside analogs, Chuma *et al.* (2009) carried out a retrospective study that involved 103 patients who underwent hepatic resection or radiofrequency ablation for initial HCC. Patients were divided into four subgroups: two groups had not received antiviral therapy (one with high serum HBV-DNA levels, the other with low HBV-DNA levels); the other two subgroups included patients who received antiviral therapy (one after HCC treatment and the other before HCC). Cumulative HCC recurrence rates at 3 years in the four subgroups were 71.1, 42.2, 42.3, and 52.0% respectively, showing that, while recurrence rate of HCC was significantly lower in the patients treated before HCC development, it was only marginally lower in those treated after HCC development than in those with high viral load. This allowed the identification of the subgroup of patients at higher risk of HCC recurrence in whom it is important to give antiviral therapy before HCC develops. Further analysis need to be carried out in a larger population of patients with HBV-related HCC and with a longer follow-up period to clarify these findings.

Conclusion

The present scientific evidence suggests that:

(1) Behavioral patterns represent an important risk factor for HBV infection and should be controlled, discouraging those favoring infection;
(2) IFN treatment seems to present a modest effect in reducing HCC risk in treated patients, but the data obtained are still far from being converted to a modification of the present guidelines for HBV infection treatment;

(3) Nucleoside analogs significantly reduce, but do not abolish, HCC risk in patients with cirrhosis; they should also be used to diminish the risk of the other potential complications of cirrhosis;
(4) Surveillance with semiannual ultrasound examination is indicated in patients with HBV-related cirrhosis as well as in other subgroups of patients, depending on racial and geographical pattern;
(5) The role of IFN in tertiary prevention of HCC relapse after radical treatment is still under debate. Some evidence in favor of the treatment is present, in patients in whom an early treatment has been adopted, but side effects due to toxicity are frequent and severe enough to limit patients' compliance substantially.

Finally, since there is definitely no agreement on the efficacy and cost/effectiveness of antiviral treatment, whether IFN or NA, in HCC prevention (Asia-Pacific Working Party, 2010; Colombo, 2010; Liaw, 2010; Zhang *et al.*, 2011), there is a need of well-constructed, large size, randomized prospective trials to confirm what is still based more on experts' opinions than on a sound scientific evidence, despite the number of studies published on the topic.

Acknowledgement

Conflicts of interest

There are no conflicts of interest.

References

Asia-Pacific Working Party on Prevention of Hepatocellular Carcinoma (2010). Prevention of hepatocellular carcinoma in the Asia-Pacific region: consensus statements. *J Gastroenterol Hepatol* **25**:657–663.

Beasley RP (2009). Rocks along the road to the control of HBV and HCC. *Ann Epidemiol* **19**:231–234.

Benvegnù L, Alberti A (2001). Patterns of hepatocellular carcinoma development in hepatitis B virus and hepatitis C virus related cirrhosis. *Antiviral Res* **52**:199–207.

Bhimma R, Coovadia HM, Adhikari M, Connolly CA (2003). The impact of the hepatitis B virus vaccine on the incidence of hepatitis B virus-associated membranous nephropathy. *Arch Pediatr Adolesc Med* **157**:1025–1030.

Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, *et al.* (2001). Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. *Gut* **48**:251–259.

Bonanni P, Pesavento G, Bechini A, Tiscione E, Mannelli F, Benucci C, *et al.* (2003). Impact of universal vaccination programmes on the epidemiology of hepatitis B: 10 years of experience in Italy. *Vaccine* **21**:685–691.

Bonino F, Oliveri F, Colombatto P, Brunetto MR (1997). Impact of interferon-alpha therapy on the development of hepatocellular carcinoma in patients with liver cirrhosis: results of an international survey. *J Viral Hepat* **4** (**Suppl 2**):79–82.

Breitenstein S, Dimitroulis D, Petrowsky H, Puhan MA, Müllhaupt B, Clavien PA (2009). Systematic review and meta-analysis of interferon after curative treatment of hepatocellular carcinoma in patients with viral hepatitis. *Br J Surg* **96**:975–981.

Bruix J, Sherman M (2005). Management of hepatocellular carcinoma. *Hepatology* **42**:1208–1236.

Bruix J, Sherman M (2011). Management of hepatocellular carcinoma: an update. *Hepatology* **53**:1020–1022.

Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, *et al.* (2001). Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* **35**:421–430.

Cabibbo G, Craxi A (2010). Epidemiology, risk factors and surveillance of hepatocellular carcinoma. *Eur Rev Med Pharmacol Sci* **14**:352–355.

Cammà C, Giunta M, Andreone P, Craxi A (2001). Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach. *J Hepatol* **34**:593–602.

Chan CY, Lee SD, Lo KJ (2004). Legend of hepatitis B vaccination: the Taiwan experience. *J Gastroenterol Hepatol* **19**:121–126.

Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, *et al.*; Taiwan Childhood Hepatoma Study Group (1997). Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* **336**:1855–1859.

Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA (2006). Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. *Am J Gastroenterol* **101**:1797–1803.

Chen CJ, Yang HI, Iloeje UH; REVEAL-HBV Study Group (2009). Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. *Hepatology* **49** (**Suppl 5**): 72–84.

Chiaramonte M, Stroffolini T, Vian A, Stazi MA, Floreani A, Lorenzoni U, *et al.* (1999). Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* **85**:2132–2137.

Chu CM (2000). Natural history of chronic hepatitis B virus infection in adults with emphasis on the occurrence of cirrhosis and hepatocellular carcinoma. *J Gastroenterol Hepatol* **15**:25–30.

Chuma M, Hige S, Kamiyama T, Meguro T, Nagasaka A, Nakanishi K, *et al.* (2009). The influence of hepatitis B DNA level and antiviral therapy on recurrence after initial curative treatment in patients with hepatocellular carcinoma. *J Gastroenterol* **44**:991–999.

Clavien PA (2007). Interferon: the magic bullet to prevent hepatocellular carcinoma recurrence after resection? *Ann Surg* **245**:843–845.

Colombo M (2010). Does chemotherapy prevent HBV-related hepatocellular carcinoma? *Cons Dig Liver Dis* **42** (**Suppl 3**):298–301.

Coppola N, Masiello A, Tonziello G, Pisapia R, Pisaturo M, Sagnelli C, *et al.* (2010). Factors affecting the changes in molecular epidemiology of acute hepatitis B in a Southern Italian area. *J Viral Hepat* **17**:493–500.

Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB (2010). Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. *Hepatology* **52**:132–141.

Di Marco V, Lo Iacono O, Camma C, Vaccaro A, Giunta M, Martorana G, *et al.* (1999). The long-term course of chronic hepatitis B. *Hepatology* **30**:257–264.

Di Marco V, Marzano A, Lampertico P, Andreone P, Santantonio T, Almasio PL, *et al.* (2004). Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine. *Hepatology* **40**:883–891.

Eun JR, Lee HJ, Kim TN, Lee KS (2010). Risk assessment for the development of hepatocellular carcinoma: according to on-treatment viral response during long-term lamivudine therapy in hepatitis B virus-related liver disease. *J Hepatol* **53**:118–125.

Fabris P, Baldo V, Baldovin T, Bellotto E, Rassu M, Trivello R, *et al.* (2008). Changing epidemiology of HCV and HBV infections in Northern Italy: a survey in the general population. *J Clin Gastroenterol* **42**:527–532.

Farinati F, Marino D, De Giorgio M, Baldan A, Cantarini M, Cursaro C (2006). Diagnostic and prognostic role of alpha-fetoprotein in hepatocellular carcinoma: both or neither? *Am J Gastroenterol* **101**:524–532.

Fattovich G, Rugge M, Brollo L, Pontisso P, Noventa F, Guido M, *et al.* (1986). Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-HBe in chronic hepatitis type B. *Hepatology* **6**:167–172.

Gresser I (2007). The antitumor effects of interferon: a personal history. *Biochimie* **89**:723–728.

Hosaka T, Suzuki F, Kobayashi M, Hirakawa M, Kawamura Y, Yastuji H, *et al.* (2010). Development of HCC in patients receiving adefovir dipivoxil for lamivudine-resistant hepatitis B virus mutants. *Hepatol Res* **40**:145–152.

Hung HF, Chen TH (2009). Probabilistic cost-effectiveness analysis of the long-term effect of universal hepatitis B vaccination: an experience from Taiwan with high hepatitis B virus infection and Hepatitis B e antigen positive prevalence. *Vaccine* **27**:6770–6776.

Ikeda K, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Fukuda M, *et al.* (1998). Interferon decreases hepatocellular carcinogenesis in patients with cirrhosis caused by the hepatitis B virus: a pilot study. *Cancer* **82**:827–835.

Ikeda K, Arase Y, Saitoh S, Kobayashi M, Suzuki Y, Suzuki F, *et al.* (2000). Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor-A prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology* **32**:228–232.

Jonasch E, Haluska FG (2001). Interferon in oncological practice: review of interferon biology, clinical applications, and toxicities. *Oncologist* **6**:34–55.

Keystone JS (2005). Travel-related hepatitis B: risk factors and prevention using an accelerated vaccination schedule. *Am J Med* **118** (**Suppl 10**):63–68.

Kim BK, Park JY, Kim do Y, Kim JK, Kim KS, Choi JS, *et al.* (2008). Persistent hepatitis B viral replication affects recurrence of hepatocellular carcinoma after curative resection. *Liver Int* **28**:393–401.

Lampertico P, Viganò M, Manenti E, Iavarone M, Sablon E, Colombo M (2007). Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. *Gastroenterology* **133**:1445–1451.

Lee CL, Hsieh KS, Ko YC (2003). Trends in the incidence of hepatocellular carcinoma in boys and girls in Taiwan after large-scale hepatitis B vaccination. *Cancer Epidemiol Biomarkers Prev* **12**:57–59.

Lencioni R (2010). Surveillance and early diagnosis of hepatocellular carcinoma. *Dig Liver Dis* **42** (**Suppl 3**):S223–S227.

Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, *et al.* (2009). Epidemiological serosurvey of hepatitis B in China – declining HBV prevalence due to hepatitis B vaccination. *Vaccine* **27**:6550–6557.

Liaw YF (2010). Does chemotherapy prevent HBV-related hepatocellular carcinoma? *Pros Dig Liver Dis* **42** (**Suppl 3**):293–297.

Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, *et al.* (2004). Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* **351**:1521–1531.

Lin SM, Sheen IS, Chien RN, Chu CM, Liaw YF (1999). Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology* **29**:971–975.

Lin SM, Yu ML, Lee CM, Chien RN, Sheen IS, Chu CM, *et al.* (2007). Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. *J Hepatol* **46**:45–52.

Lo CM, Liu CL, Chan SC, Lam CM, Poon RT, Ng IO, *et al.* (2007). A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. *Ann Surg* **245**:831–842.

Lok AS (2004). Prevention of hepatitis B virus-related hepatocellular carcinoma. *Gastroenterology* **127** (**Suppl 1**):303–309.

Majori S, Baldo V, Tommasi I, Malizia M, Floreani A, Monteiro G, *et al.* (2008). Hepatitis A, B, and C infection in a community of sub-Saharan immigrants living in Verona (Italy). *J Travel Med* **15**:323–327.

Mariano A, Mele A, Tosti ME, Parlato A, Gallo G, Ragni P, *et al.* (2004). Role of beauty treatment in the spread of parenterally transmitted hepatitis viruses in Italy. *J Med Virol* **74**:216–220.

Matsumoto A, Tanaka E, Rokuhara A, Kiyosawa K, Kumada H, Omata M, *et al.* (2005). Efficacy of lamivudine for preventing hepatocellular carcinoma in chronic hepatitis B: a multicenter retrospective study of 2795 patients. *Hepatol Res* **32**:173–184.

Mazzaferro V, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, *et al.* (2006). Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology* **44**:1543–1554.

Mirici-Cappa F, Gramenzi A, Santi V, Zambruni A, Di Micoli A, Frigerio M, *et al.* (2010). Treatments for hepatocellular carcinoma in elderly patients are as effective as in younger patients: a 20-year multicentre experience. *Gut* **59**:387–396.

Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A (2010). Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. *J Hepatol* **53**:348–356.

Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP (2006). The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* **45**:529–538.

Plymoth A, Viviani S, Hainaut P (2009). Control of hepatocellular carcinoma through hepatitis B vaccination in areas of high endemicity: perspectives for global liver cancer prevention. *Cancer Lett* **286**:15–21.

Qu LS, Jin F, Huang XW, Shen XZ (2010). High hepatitis B viral load predicts recurrence of small hepatocellular carcinoma after curative resection. *J Gastrointest Surg* **14**:1111–1120.

Romeo R, Del Ninno E, Rumi M, Russo A, Sangiovanni A, de Franchis R, *et al.* (2009). A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology* **136**:1629–1638.

Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, *et al.* (2010). Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. *J Hepatol* **53**:291–297.

Sherman M (2010). The resurrection of alphafetoprotein. *J Hepatol* **52**:939–940.

Stroffolini T, Sagnelli E, Mele A, Almasio P (2005). Trends of aetiological factors of hepatocellular carcinoma in Italy. *Dig Liver Dis* **37**:985–986.

Sun HC, Tang ZY, Wang L, Qin LX, Ma ZC, Ye QH, *et al.* (2006). Postoperative interferon alpha treatment postponed recurrence and improved overall survival in patients after curative resection of HBV-related hepatocellular carcinoma: a randomized clinical trial. *J Cancer Res Clin Oncol* **132**: 458–465.

Sung JJ, Tsoi KK, Wong VW, Li KC, Chan HL (2008). Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. *Aliment Pharmacol Ther* **28**:1067–1077.

Tafuri S, Prato R, Martinelli D, Melpignano L, De Palma M, Quarto M, *et al.* (2010). Prevalence of hepatitis B, C, HIV and syphilis markers among refugees in Bari, Italy. *BMC Infect Dis* **10**:213.

Trevisani F, De NS, Rapaccini G, Farinati F, Benvegnù L, Zoli M, *et al.* (2002). Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). *Am J Gastroenterol* **97**:734–744.

Trevisani F, Cantarini MC, Labate AM, De Notariis S, Rapaccini G, Farinati F, *et al.* (2004). Surveillance for hepatocellular carcinoma in elderly Italian patients with cirrhosis: effects on cancer staging and patient survival. *Am J Gastroenterol* **99**:1470–1476.

Trevisani F, Santi V, Gramenzi A, Di Nolfo MA, Del Poggio P, Benvegnù L, *et al.* (2007). Surveillance for early diagnosis of hepatocellular carcinoma: is it effective in intermediate/advanced cirrhosis? *Am J Gastroenterol* **102**: 2448–2457.

Viviani S, Jack A, Hall AJ, Maine N, Mendy M, Montesano R, *et al.* (1999). Hepatitis B vaccination in infancy in The Gambia: protection against carriage at 9 years of age. *Vaccine* **17**:2946–2950.

Wichajarn K, Kosalaraksa P, Wiangnon S (2008). Incidence of hepatocellular carcinoma in children in Khon Kaen before and after national hepatitis B vaccine program. *Asian Pac J Cancer Prev* **9**:507–509.

Wu JC, Huang YH, Chau GY, Su CW, Lai CR, Lee PC, *et al.* (2009). Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma. *J Hepatol* **51**:890–897.

Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, *et al.*; Taiwan Community-based Cancer Screening Project (2002). Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* **347**:168–174.

Yang YF, Zhao W, Zhong YD, Xia HM, Shen L, Zhang N (2009). Interferon therapy in chronic hepatitis B reduces progression to cirrhosis and hepatocellular carcinoma: a meta-analysis. *J Viral Hepat* **16**:265–271.

Yuen MF, Hui CK, Cheng CC, Wu CH, Lai YP, Lai CL (2001). Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: the effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. *Hepatology* **34**:139–145.

Yuen MF, Seto WK, Chow DH, Tsui K, Wong DK, Ngai VW, *et al.* (2007). Long-term lamivudine therapy reduces the risk of long-term complications of chronic hepatitis B infection even in patients without advanced disease. *Antivir Ther* **12**:1295–1303.

Zanetti AR, Van Damme P, Shouval D (2008). The global impact of vaccination against hepatitis B: a historical overview. *Vaccine* **26**:6266–6273.

Zhang BH, Yang BH, Tang ZY (2004). Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* **130**: 417–422.

Zhang CH, Xu GL, Jia WD, Li JS, Ma JL, Ge YS (2011). Effects of interferon treatment on development and progression of hepatocellular carcinoma in patients with chronic virus infection: a meta-analysis of randomized controlled trials. *Int J Cancer* [Epub ahead of print].