PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

ELSEVIER

World J Gastroenterol 2005;11(47):7391-7400
World Journal of Gastroenterology ISSN 1007-9327

• *REVIEW* •

Hepatocellular carcinoma: Therapy and prevention

Hubert E Blum

Hubert E Blum, Department of Medicine II, University of Freiburg, D-79106 Freiburg, Germany
Correspondence to: Hubert E Blum, MD, Department of Medicine II, University of Freiburg, Hugstetter Strasse 55, D-79106 Freiburg, Germany. hubert.blum@uniklinik-freiburg.de
Telephone: +49-761-270-3404 Fax: +49-761-270-3610
Received: 2004-12-22 Accepted: 2005-03-10

Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide. The major etiologies and risk factors for the development of HCC are well defined and some of the multiple steps involved in hepatocarcinogenesis have been elucidated in recent years. Despite these scientific advances and the implementation of measures for the early detection of HCC in patients at risk, patient survival has not improved during the last three decades. This is due to the advanced stage of the disease at the time of clinical presentation and limited therapeutic options. The therapeutic options fall into five main categories: surgical interventions including tumor resection and liver transplantation, percutaneous interventions including ethanol injection and radiofrequency thermal ablation, transarterial interventions including embolization and chemoembolization, radiation therapy and drugs as well as gene and immune therapies. These therapeutic strategies have been evaluated in part in randomized controlled clinical trials that are the basis for therapeutic recommendations. Though surgery, percutaneous and transarterial interventions are effective in patients with limited disease (1-3 lesions, <5 cm in diameter) and compensated underlying liver disease (cirrhosis Child A), at the time of diagnosis more than 80% patients present with multicentric HCC and advanced liver disease or comorbidities that restrict the therapeutic measures to best supportive care. In order to reduce the morbidity and mortality of HCC, early diagnosis and the development of novel systemic therapies for advanced disease, including drugs, gene and immune therapies as well as primary HCC prevention are of paramount importance. Furthermore, secondary HCC prevention after successful therapeutic interventions needs to be improved in order to make an impact on the survival of patients with HCC. New technologies, including gene expression profiling and proteomic analyses, should allow to further elucidate the molecular events underlying HCC development and to identify novel diagnostic markers as well as therapeutic and preventive targets.

Key words: HCC resection; Liver transplantation; Percutaneous ethanol injection; Radiofrequency thermal ablation; Transarterial embolization or chemoembolization; Chemotherapy; Gene therapy; Immune therapy; Prevention

Blum HE. Hepatocellular carcinoma: Therapy and prevention. *World J Gastroenterol* 2005; 11(47): 7391-7400
http://www.wignet.com/1007-9327/11/7391.asp

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide[1-10]. The incidence ranges from <10 cases per 100 000 persons in North America and Western Europe to 50-150 cases per 100 000 persons in parts of Africa and Asia, where HCC is responsible for a large number of cancer deaths. However, a rise in the incidence and mortality of HCC, most likely reflecting the increased prevalence of hepatitis C virus (HCV) infection, has recently been observed in most industrialized countries[11-14].

The major etiologies of HCC are well defined (Table 1). An elevated body mass index, especially in men[15], and diabetes mellitus[9] are included among the well-known factors. Some of the steps involved in the molecular pathogenesis of HCC have been elucidated in the recent years. As for most types of cancer, hepatocarcinogenesis is a multistep process involving different genetic alterations that ultimately lead to the malignant transformation of hepatocytes. While significant progress has been made in recognizing the sequence of events involved in other forms of cancer, most notably in colorectal cancer and certain hematopoietic malignancies, the molecular contribution of the multiple factors and their interactions in hepatocarcinogenesis are still poorly understood. HCCs are phenotypically (morphology and microscopy) and genetically heterogenous tumors, possibly reflecting in part the heterogeneity of etiologic factors implicated in HCC development, the complexity of hepatocyte functions and the late stage at which HCCs usually become clinically symptomatic and detectable. Malignant transformation of hepatocytes may occur regardless of the etiologic agent through a pathway of increased liver cell turnover, induced by chronic liver injury and regeneration in a context of inflammation, immune response, and oxidative DNA damage. This may result in genetic alterations, such as activation of cellular oncogenes, inactivation of tumor suppressor genes, possibly in cooperation with genomic instability, including

Table 1 Major etiologies of HCC

Chronic viral hepatitis B, C, D
Toxins (e.g., alcohol, aflatoxins)
Hereditary metabolic liver diseases (e.g., hereditary hemochromatosis, α-1-antitrypsin deficiency)
Autoimmune hepatitis
Overweight, especially in males, and diabetes mellitus; nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD)

Table 2 Okuda stages I-III of HCC

Tumor mass	<50% of liver	⩾50% of liver
Ascites	No	Yes
Albumin (g/L)	>3	⩽3
Bilirubin (mg/dL)	<3	⩾3
Points	0	1
Stage I	0 points	
Stage II	1-2 points	
Stage III	3-4 points	

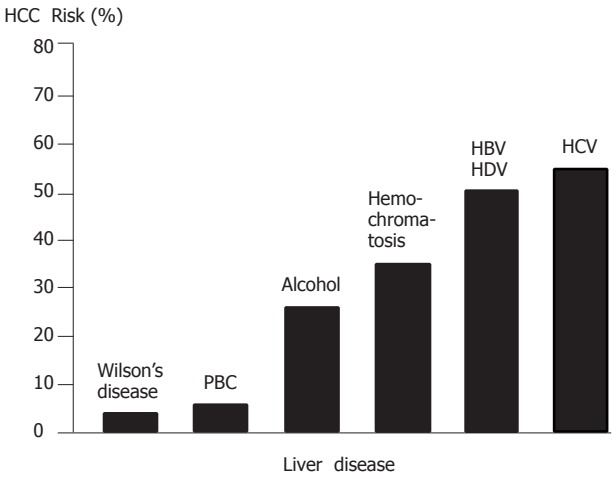

Figure 1 HCC Risk in Liver Cirrhosis

DNA mismatch repair defects and impaired chromosomal segregation, overexpression of growth and angiogenic factors, and telomerase activation[16-23]. Chronic viral hepatitis B, C, and D, alcohol, metabolic liver diseases such as hemochromatosis and α-1-antitrypsin deficiency as well as non-alcoholic fatty liver disease may act predominantly through this pathway of chronic liver injury, regeneration and cirrhosis. Accordingly, the major clinical risk factor for the development of HCC is liver cirrhosis since 70-90% of HCCs develop into a cirrhotic liver. Most HCCs occur after many years of chronic hepatitis that provides the mitogenic and mutagenic environments to precipitate random genetic alterations resulting in the malignant transformation of hepatocytes and HCC development.

The HCC risk in patients with liver cirrhosis depends on the activity, duration and etiology of the underlying liver disease (Figure 1). Clinical and biological variables (age, anti-HCV positivity, PTT and platelet count) allow to further identify a subset of cirrhotic patients with the highest risk of HCC development[24]. Coexistence of etiologies, such as hepatitis B virus (HBV) and HCV infection, HBV infection and aflatoxin B1[23,25], HBV/HCV infection and alcohol or diabetes mellitus[26], or HCV infection and liver steatosis[27], increases the relative risk of HCC development. Also, occult HBV infection (anti-HBc positive only) carries a significant HCC risk[28,29]. In general, HCCs are more frequent in males than in females and the incidence increases with age. On the other hand, there is evidence that HBV and possibly HCV under certain circumstances play an additional direct role in the molecular pathogenesis of HCC. Finally, aflatoxins can induce mutations of the p53 tumor suppressor gene, thus pointing to the contribution of an environmental factor to tumor development at the molecular level. Furthermore, in a transgenic mouse model it has been shown that chronic immune-mediated liver cell injury without environmental or infectious agents is sufficient to cause HCC[30] and that inhibition of cytotoxic T lymphocyte-induced apoptosis and chronic inflammation by neutralization of the Fas ligand and prevents HCC development in this model[31]. In addition, in a transgenic mouse model it has been demonstrated that NF-κB may be the link between inflammation and HCC development[32,33]. Finally, individual polymorphisms of drug-metabolizing enzymes, such as cytochrome P450 oxidases, N-acetyltransferases and glutathione-*S*-transferase, may contribute to the genetic susceptibility to HCC development[34].

HCC screening, staging, and natural course

For the staging of HCCs, five systems have been proposed for the assessment of the extent and prognosis of the disease[35,36]: the Okuda staging system (Table 2)[37], the TNM classification and its modification by the Union International Contre Cancer (UICC), the Barcelona Clinic Liver Cancer (BCLC) classification[38] and the Cancer of the Liver Italian Program (CLIP) score[39]. The Okuda staging system is very effective for the identification of a subgroup of patients (Okuda III) with a very good prognosis of patients who should be treated with best supportive care (BSC) only. The BCLC classification appears especially useful for the selection of treatment but has not been independently validated. The CLIP score is superior to the Okuda staging system but has not been systematically assessed in patients undergoing resection or liver transplantation. Thus, one staging system is not clearly superior to the others. The natural course of the disease and the median survival of patients with HCC depend on the stage of the disease at the time of diagnosis. In patients with CLIP score 0 or Okuda stage I, the median survival is in the range of 23-69 mo, while in patients with CLIP score 3-5 or Okuda stage III, the median survival is only 1-14 mo[4]. The staging system is clinically most important for the appropriate choice of therapeutic strategy for individual patients.

Treatment of HCC

Therapies for HCC can be divided into four categories: surgical interventions (tumor resection and liver

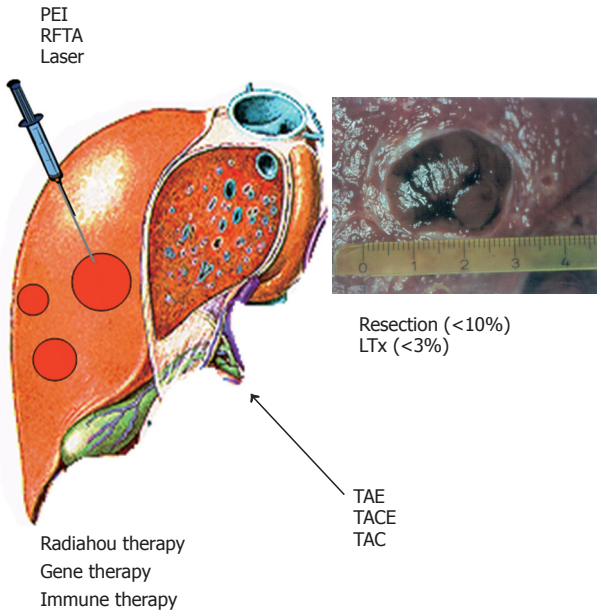

Figure 2 HCC treatment.

transplantation), percutaneous interventions (ethanol injection, radiofrequency thermal ablation), transarterial interventions (embolization, chemoperfusion, or chemoembolization) and drugs including gene and immune therapy (Figure 2). Potentially curative therapies are tumor resection, liver transplantation, and percutaneous interventions that can result in complete responses and improved survival in a large number of patients. In selected cases, transarterial interventions result in palliation with good response rates and improved survival in some cases. Drugs as well as conventional radiotherapy have no proven efficacy.

Till date, surgical, percutaneous and transarterial interventions have not been compared in randomized controlled trials. Tumor resection and transplantation can achieve a 5-year survival rate of 60-70% in selected patients transplantation is the best treatment for patients with single lesions and advanced liver diseases, such as decompensated cirrhosis and multicentric small tumors. Percutaneous interventions, again in selected patients, result in a 5-year survival rate of 40-50%. The following different therapeutic options as well as primary and secondary HCC prevention are discussed in detail.

Surgical interventions

Resection in patients without concomitant liver cirrhosis (5% in Western countries, 40% in Sub-Sahara Africa and Asia), HCC resection is the treatment of choice with a low rate of life-threatening complications. By comparison, in the majority of patients with cirrhosis, strict selection is required to avoid resection-related complications, especially postoperative liver failure[40]. Apart from bilirubin and albumin concentration as well as platelet count and indocyanine green clearance[14,42], a recent study has identified an elevated serum concentration of 7s-collagen as an independent risk factor for postoperative liver failure[43].

Resection-related mortality should be <1-3%, and the 5-year survival rate should be >50%. In patients with normal liver function (normal indocyanine green retention rate and bilirubin level), absence of clinically relevant portal hypertension (hepatic venous pressure gradient <1.33 kpa, no esophageal varices, no splenomegaly, platelet count $>100\times10^9$/L) and one asymptomatic HCC lesion only, the 5-year survival rate of 70% can be achieved. By comparison in patients with clinically relevant portal hypertension, the 5-year survival rate is about 50% only and in patients with portal hypertension and evidence of impaired liver function, the 5-year survival rate is even lower.

After successful HCC resection, tumor recurrence in the cirrhotic liver (local recurrence as well as *de novo* tumors) in about 70% of patients after 5 years is a major clinical problem. The risk of recurrence is especially high in patients with microvascular invasion and/or additional tumor nodules[41,44]. Therefore, strategies aimed at secondary HCC prevention are of paramount importance.

Liver transplantation Liver transplantation is in principle the optimal therapeutic option for HCCs, because it simultaneously removes the tumor and the underlying cirrhosis, including the risk of HCC recurrence[40,45-47]. While broad selection criteria applied previously led to poor results with the recurrence rate of about 50% and the 5-year survival rate <40%, the current criteria for liver transplantation in patients with HCC (1 lesion <5 cm in diameter or maximum 3 lesions <3 cm in diameter) result in the 5-year survival rate of 70% or more and the recurrence rate <15%[48-50]. Possibly these criteria can be extended in future, depending on more experiences based on the stage of the disease, macrovascular invasion, histopathological characteristics (histopathology, aneuploidy, microvascular invasion) as well as DNA and RNA chip data (molecular signature, proteomic signature and others)[51,52].

Clinically, it is most important to shorten the waiting time for transplantation to <6 mo. This is difficult to achieve with cadaveric liver transplantation due to the shortage of donors. With a waiting time of >12 mo in some Western countries, the drop-out rate of patients is 20-50%. To bridge the time to transplantation and to prevent tumor progression, neoadjuvant treatments, such as percutaneous and transarterial interventions may lead to an improved outcome[53]. While marginal livers, domino donors, and split liver transplantation have no major impact, living donor liver transplantation has been shown to be an alternative to cadaveric liver transplantation. Around 3 000 interventions have been done worldwide. However, living donor liver transplantation is a complex procedure with a morbidity of 20-40% and a donor mortality of 0.3-0.5%[50,54,55]. Therefore, a very careful selection of patients and donors, including consideration of ethical, societal and legal issues is central to the successful implementation of living donor liver transplantation for the treatment of HCC patients[56].

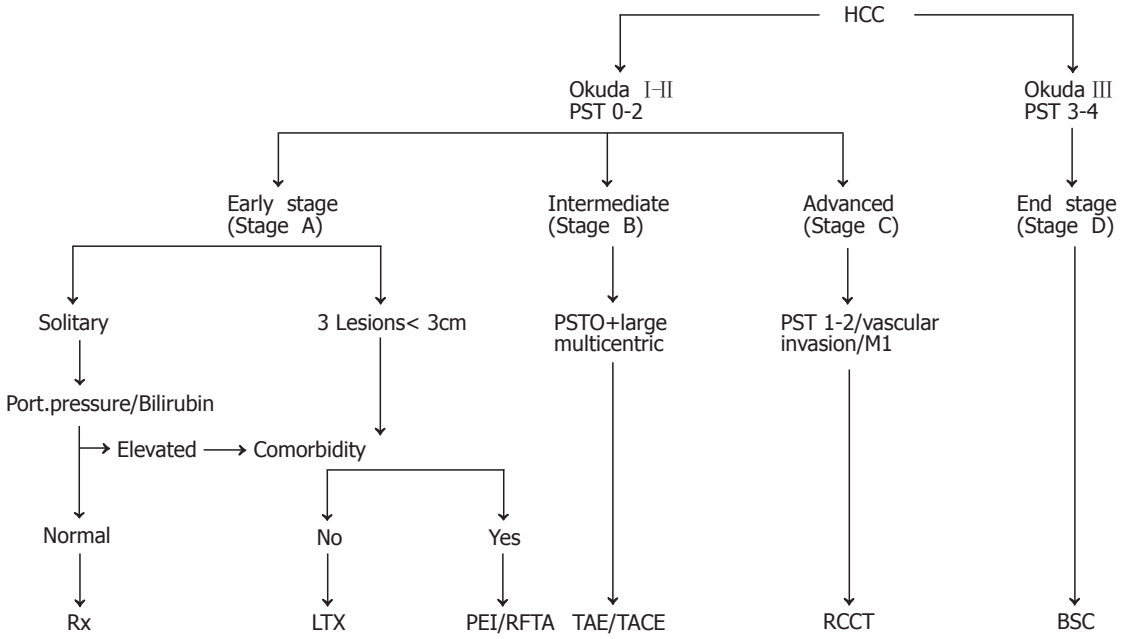

Figure 3 Stage-Dependent HCC Treatment.

Percutaneous interventions

Percutaneous intervention is the best option for small unresectable HCCs[57-59]. Tumor ablation can be achieved chemically by percutaneous ethanol injection (PEI) or acetic acid injection (PAI) or thermally by radiofrequency thermal ablation (RFTA), microwave heat-induced thermotherapy (HiTT), laser-induced thermotherapy (LiTT), or cryoablation. Apart from percutaneous interventions, these techniques can be applied also laparoscopically or after laparotomy.

Percutaneous ethanol injection PEI is the most widely used technique[60,61]. It is safe, easy to perform, inexpensive and can achieve complete tumor response rate of 90-100% in HCCs smaller than 2 cm in diameter, 70% in HCCs (3 cm in diameter) and 50% in HCCs (5 cm in diameter). Patients with liver cirrhosis Child A with complete responses can achieve a 5-year survival rate of 50% or more. Therefore, PEI is the procedure of choice for patients with a single HCC lesion smaller than 5 cm in diameter or with up to three lesions smaller than 3 cm in diameter (Figure 3).

Radiofrequency thermal ablation RFTA is an alternative to PEI[58,59,62,63]. Several devices are available that can be applied percutaneously, laparoscopically, or during laparotomy. The efficacy of RFTA is similar to that of PEI but requires generally only a single session. While being more expensive than PEI, RFTA offers a better local tumor control and a potential advantage of allowing the ablation of tumors larger than 5 cm in diameter especially when newer generation devices are used. However, the 5-year survival rate after complete response to RFTA is currently similar to that of PEI (around 30-40%) depending on the child stage of the underlying liver cirrhosis. In a review of 3 670 patients treated with RFTA, the mortality is 0-5% and the complication rate is 8-9%[64]. Predictors of treatment response are tumor size and morphology (well encapsulated *vs* invasive).

Percutaneous HCC ablation by PEI and/or RFTA when considered together is an effective treatment for patients with HCCs that prolongs the tumor-free and overall survival time, especially if surgery is not feasible. This strategy has been evaluated also for the treatment of liver metastases[65].

Transarterial interventions

Transarterial embolization and chemoembolization are the most widely used treatments for HCCs which are unresectable or cannot be effectively treated with percutaneous interventions[66-69]. Embolization agents may be administered alone (embolization) or after selective intra-arterial chemotherapy (generally doxorubicin, mitomycin or cisplatin) or in combination with lipiodol (chemoembolization). Transarterial embolization or chemoembolization results in partial responses in 15-55% of patients, delays tumor progression and vascular invasion, and prolongs the survival time compared to conservative management. The most important aspect is the selection of patients, i.e., patients should have preserved liver function (Child A) and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread[67,69]. In patients with advanced liver disease (Child B or C), treatment-induced liver failure may offset the antitumor effect or survival benefit of the intervention. As has been shown recently, postoperative adjuvant TACE may improve survival in patients with risk factors for residual tumor[70].

Radiation therapy

While radiotherapy plays only a minor role in the treatment of primary HCC, selective intra-arterial

Table 3 Drugs evaluated in clinical trials for the treatment of patients with HCC

5-Fluorouracil
Capecitabine
Doxorubicin
Epirubicin
Etoposide
Cisplatin
Gemcitabine
Mitoxantrone
Interferon alpha
Megestrol acetate
Tamoxifen
Octreotide
Thalidomide
Thymophysin
α-1-thymosin

injection of ^{131}iodine-labeled lipiodol has been performed in some patients[71] but needs further clinical evaluation before a recommendation can be made. Furthermore, high dose proton beam radiotherapy and external beam radiation as well as Yttrium-90 microsphere treatment have been recently explored in clinical trials in patients with unresectable HCC[72-74]. These strategies will certainly be further explored in clinical studies and may become a treatment option in future.

Drugs

A number of chemotherapeutic, hormonal and other drugs (Table 3) have been evaluated in clinical trials[75-77]. While most chemotherapeutic agents, such as tamoxifen[78], octreotide[79] and interferon[66], have not been shown to be effective in randomized controlled clinical trials, there are a number of substances that may deserve further clinical evaluation, such as gemcitabine[80,81], thymostimulin[82], α-1-thymosin[83], pravastatin[84], thalidomide[85] and megestrol acetate[86], antiangiogenic small molecules, Cox-2 inhibitors in combination with capecitabine and possibly others. Till date, however, none of these drugs can be recommended outside clinical studies.

Experimental strategies

In view of the limited therapeutic options for advanced HCCs, a number of experimental strategies are being evaluated (Figure 4), including gene and immune therapies based on suicide, cytokine and antiangiogenic genes or DNA vaccination with tumor-specific genes[87-90], oncolytic viruses[91] as well as novel drugs such as 3-bromopyruvate[92].

HCC prevention

HCC prevention falls into two categories. Primary prevention that is aimed at the prevention of HCC development in patients with chronic liver diseases of different etiologies and secondary prevention that is aimed at preventing the recurrence and/or the development of new HCC lesions after successful surgical or non-surgical HCC treatment[93,94].

Primary HCC prevention Primary prevention is aimed at the interference with HCC development at four stages (Figure 5).

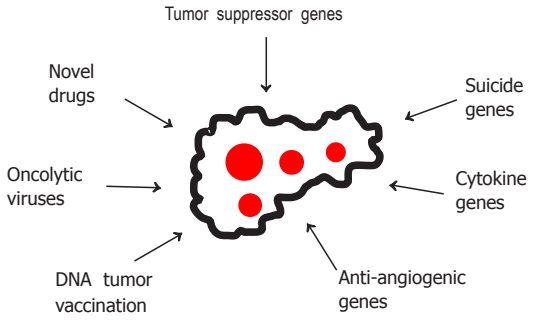

Figure 4 HCC Experimental Therapeutic Strategies

Stage 1: Interventions at this step are aimed at the prevention of acquired liver diseases. Apart from avoiding liver toxins, including alcohol and certain drugs, or infections with HBV or HCV by hygienic measures, avoiding parenteral exposure to blood, blood products or contaminated needles etc., a prime example is vaccination against HBV infection using commercially available active and passive vaccines. Several HBV vaccines using natural or recombinant hepatitis B surface antigen (HBsAg) from different sources are well introduced in clinical practice and universal vaccination in Taiwan has indeed already resulted in a decline of the incidence of HCCs[95]. In addition, novel HBV vaccination strategies are being explored, including a novel triple HBsAg recombinant vaccine[96], epidermal HBsAg powder immunization[97] as well as oral immunization using HBsAg transgenic plants[98-100]. Furthermore, DNA vaccination has been shown in animal models to induce antibodies against HBsAg/anti-HBs[101,102] even after topical application to the skin. For the prevention of HCV infection, however no effective vaccine is available till date. While several HCV vaccination concepts are being evaluated, including HCV proteins[103], HCV-like particles[104] as well as intravenous, intrahepatic, intraepidermal, intramuscular or oral cDNA immunization[105-109], it is not expected that a vaccine against HCV infection will become commercially available within the next few years.

Stage 2: Interventions at this step are aimed at the early treatment of acute liver diseases, thereby blocking their transition into chronic hepatitis that carries the risk of developing liver cirrhosis and its sequelae, including HCC development. While the principles mentioned above regarding liver toxins can also be applied here, the early diagnosis and treatment of inherited liver diseases, such as Wilson's disease and hemochromatosis, are of paramount importance. Furthermore, recent studies suggest that early treatment of acute HCV infection prevents its progression to chronic hepatitis C[110-112].

Stage 3: Interventions at this step are aimed at the prevention of the progression of chronic hepatitis to liver cirrhosis that carries a high risk of HCC development. Apart from avoiding liver toxins and long-term use of high dose androgens or other anabolic steroids, the treatment

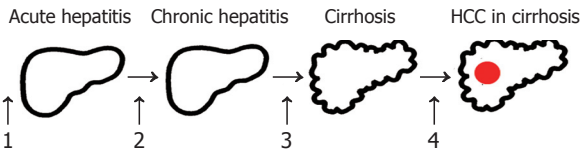

Figure 5 Primary HCC Prevention.

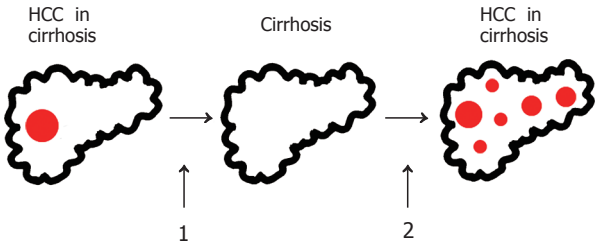

Figure 6 Secondary HCC Prevention.

of chronic hepatitis is of paramount importance. This includes the treatment of inherited, cholestatic or autoimmune liver diseases as well as the treatment of chronic viral hepatitis B or C. Reduction of iron overload by phlebotomy, for example, has been shown to stop the progression of hemochromatosis to liver cirrhosis and HCC. Treatment of chronic hepatitis B with interferon alpha or nucleoside analogs[113-118] and chronic hepatitis C with interferon alpha and now the combination of interferon alpha and ribavirin has demonstrated biochemical, virological, and histopathological improvements[119-123] and a lower incidence of HCC development[124-126].

Stage 4: Interventions at this step are aimed at interfering with the molecular events leading to HCC development, usually in a cirrhotic liver. These strategies include all treatment modalities detailed above (stage 3) as far as they can be implemented in patients with compensated or decompensated liver cirrhosis. In addition, some of the measures to prevent HCC recurrence after successful HCC treatment (secondary prevention) should in principle be useful for HCC prevention at this stage of the disease. Furthermore, some concepts of molecular therapy of HCCs should be applicable also in the prevention of HCCs. Without experimental pre-clinical data on these issues, it would be premature to discuss their potential clinical impact.

Secondary HCC prevention The prevention of a local recurrence and/or the development of new HCC lesions in patients after successful surgical or non-surgical HCC treatment (Figure 6) is of paramount importance and can significantly improve disease-free and overall patient survival.

After successful HCC resection or non-surgical ablation, HCC recurrence in the remaining cirrhotic liver is the major limitation of life expectancy of these patients. The probability of recurrence is about 50% within 3 years after successful treatment[38,127]. Strategies to prevent HCC recurrence are therefore central to the improvement of survival of HCC patients after initial cure. Apart from liver transplantation after successful resection[44], the strategies explored to date include administration of polyprenoic acid (an acyclic retinoid)[128] interferon alpha[129] and interferon beta[130]. Furthermore, adoptive immunotherapy[131] and intra-arterial injection of ^{131}iodine-labeled lipiodol[132,133] have been evaluated in clinical studies. All these interventions can result in lower HCC recurrence rates. These findings have to be confirmed in larger randomized controlled studies, demonstrating that a clear clinical benefit before secondary prevention with one of the strategies mentioned above should enter clinical practice.

Summary and perspectives

HCC is one of the most common malignant tumors in some areas of the world with an extremely poor prognosis HCC treatment is based on randomized controlled trials and many observational studies. Treatment options fall into four main categories: surgical interventions including tumor resection and liver transplantation, percutaneous interventions including ethanol injection and RFTA, transarterial interventions including embolization and chemoembolization, and drugs as well as gene and immune therapies. Though surgery as well as percutaneous and transarterial interventions are effective in patients with limited disease (up to three lesions smaller than 3 cm in diameter or one lesion smaller than 5 cm in diameter) and compensated underlying liver disease (cirrhosis Child A), at the time of diagnosis more than 80% patients present with multicentric HCC and advanced liver disease or co-morbidities that restrict the therapeutic measures to BSC.

In order to reduce the morbidity and mortality of HCC, early diagnosis and the development of novel systemic therapies for advanced disease, including drugs, gene and immune therapies as well as primary HCC prevention are of paramount importance. Furthermore, secondary HCC prevention after successful therapeutic interventions needs to be improved in order to achieve better survival of patients with HCC. New technologies, including gene expression profiling and proteomic analyses, should allow to further elucidate the molecular events underlying HCC development and to identify novel diagnostic markers as well as therapeutic and preventive targets.

REFERENCES

1 **Okuda K.** Hepatocellular carcinoma. *J Hepatol* 2000; **32**: 225-237
2 **Bruix J,** Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodes J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430
3 **Bruix J,** Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology* 2002; **35**: 519-524
4 **Befeler AS,** Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. *Gastroenterology* 2002; **122**: 1609-1619
5 **Llovet JM,** Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907-1917
6 **Llovet JM,** Fuster J, Bruix J. The Barcelona approach: diagnosis, staging and treatment of hepatocellular carcinoma. *Liver Transpl* 2004; **10**: S115-S120

7 **Bruix J,** Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S179-S188
8 **Kiyosawa K,** Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Gad A, Tanaka E. Hepatocellular carcinoma: recent trends in Japan. *Gastroenterology* 2004; **127**: S17-S26
9 **El-Serag HB.** Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology* 2004; **127**: S27-S34
10 **Fattovich G,** Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35-S50
11 **Taylor-Robinson SD,** Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK, 1979-1994. Lancet 1997; 350: 1142-1143
12 **Deuffic S,** Poynard T, Buffat L, Valleron AJ. Trends in primary liver cancer. *Lancet* 1998; **351**: 214-215
13 **El-Serag HB,** Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999; **340**: 745-750
14 **El-Serag HB,** Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med* 2003; **139**: 817-823
15 **Calle EE,** Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003; 348: 1625-1638
16 **Ozturk M.** Genetic aspects of hepatocellular carcinogenesis. *Semin Liver Dis* 1999; 19: 235-242
17 **Bergsland EK.** Molecular mechanisms underlying the development of hepatocellular carcinoma. *Semin Oncol* 2001; 28: 521-531
18 **Thorgeirsson SS,** Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. *Nat Genet* 2002; **31**: 339-346
19 **Block TM,** Mehta AS, Fimmel CJ, Jordan R. Molecular viral oncology of hepatocellular carcinoma. *Oncogene* 2003; **22**: 5093-5107
20 **Suriawinata A,** Xu R. An update on the molecular genetics of hepatocellular carcinoma. *Semin Liver Dis* 2004; **24**: 77-88
21 **Satyanarayana A,** Manns MP, Rudolph KL. Telomeres and telomerase: a dual role in hepatocarcinogenesis. *Hepatology* 2004; **40**: 276-283
22 **Bréchot C.** Pathogenesis of hepatitis B virus-related hepatocellular carcinoma: old and new paradigms. *Gastroenterology* 2004; **127**: S56-S61
23 **Yu MC,** Yuan JM. Environmental factors and risk for hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S72-78
24 **Velázquez RF,** Rodríguez M, Navascués CA, Linares A, Pérez R, Sotorríos NG, Martínez I, Rodrigo L. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology* 2003; **37**: 520-527
25 **Ming L,** Thorgeirsson SS, Gail MH, Lu P, Harris CC, Wang N, Shao Y, Wu Z, Liu G, Wang X, Sun Z. Dominant role of hepatitis B virus and cofactor role of aflatoxin in hepatocarcinogenesis in Qidong, China. *Hepatology* 2002; **36**: 1214-1220
26 **Hassan MM,** Hwang LY, Hatten CJ, Swaim M, Li D, Abbruzzese JL, Beasley P, Patt YZ. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology* 2002; **36**: 1206-1213
27 **Ohata K,** Hamasaki K, Toriyama K, Matsumoto K, Saeki A, Yanagi K, Abiru S, Nakagawa Y, Shigeno M, Miyazoe S, Ichikawa T, Ishikawa H, Nakao K, Eguchi K. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer* 2003; **97**: 3036-3043
28 **Yano Y,** Yamashita F, Sumie S, Ando E, Fukumori K, Kiyama M, Oyama T, Kuroki S, Kato O, Yamamoto H, Tanaka M, Sata M. Clinical features of hepatocellular carcinoma seronegative for both HBsAg and anti-HCV antibody but positive for anti-HBc antibody in Japan. *Am J Gastroenterol* 2002; **97**: 156-161
29 **Pollicino T,** Squadrito G, Cerenzia G, Cacciola I, Raffa G, Craxi A, Farinati F, Missale G, Smedile A, Tiribelli C, Villa E, Raimondo G. Hepatitis B virus maintains its pro-oncogenic properties in the case of occult HBV infection. *Gastroenterology* 2004; **126**: 102-110
30 **Nakamoto Y,** Guidotti LG, Kuhlen CV, Fowler P, Chisari FV. Immune pathogenesis of hepatocellular carcinoma. *J Exp Med* 1998; **188**: 341-350
31 **Nakamoto Y,** Kaneko S, Fan H, Momoi T, Tsutsui H, Nakanishi K, Kobayashi K, Suda T. Prevention of hepatocellular carcinoma development associated with chronic hepatitis by anti-fas ligand antibody therapy. *J Exp Med* 2002; **196**: 1105-1111
32 **Pikarsky E,** Porat RM, Stein I, Abramovitch R, Amit S, Kasem S, Gutkovich-Pyest E, Urieli-Shoval S, Galun E, Ben-Neriah Y. NF-kappaB functions as a tumour promoter in inflammation-associated cancer. *Nature* 2004; **431**: 461-466
33 **Balkwill F,** Coussens LM. Cancer: an inflammatory link. *Nature* 2004; **431**: 405-406
34 **Chen CJ,** Chen DS. Interaction of hepatitis B virus, chemical carcinogen, and genetic susceptibility: multistage hepatocarcinogenesis with multifactorial etiology. *Hepatology* 2002; **36**: 1046-1049
35 **Di Bisceglie AM.** Screening for hepatocellular carcinoma: being old is not all bad. *Am J Gastroenterol* 2004; 99: 1477-1478
36 **Talwalkar JA,** Gores GJ. Diagnosis and staging of hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S126-S132
37 **Okuda K,** Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, Nakajima Y, Ohnishi K. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985; **56**: 918-928
38 **Llovet JM,** Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329-338
39 **Farinati F,** Rinaldi M, Gianni S, Naccarato R. How should patients with hepatocellular carcinoma be staged? Validation of a new prognostic system. *Cancer* 2000; **89**: 2266-2273
40 **Song TJ,** Ip EW, Fong Y. Hepatocellular carcinoma: current surgical management. *Gastroenterology* 2004; **127**: S248-S260
41 **Llovet JM,** Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999; **30**: 1434-1440
42 **Arii S,** Yamaoka Y, Futagawa S, Inoue K, Kobayashi K, Kojiro M, Makuuchi M, Nakamura Y, Okita K, Yamada R. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. *Hepatology* 2000; **32**: 1224-1229
43 **Kubo S.** Neuer Marker für Leberversagen nach Resektion. *Ann Surg* 2004; **239**: 186-193
44 **Sala M,** Fuster J, Llovet JM, Navasa M, Solé M, Varela M, Pons F, Rimola A, García-Valdecasas JC, Brú C, Bruix J. High pathological risk of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. *Liver Transpl* 2004; **10**: 1294-1300
45 **Wiesner RH,** Freeman RB, Mulligan DC. Liver transplantation for hepatocellular cancer: the impact of the MELD allocation policy. *Gastroenterology* 2004; **127**: S261-S267
46 **Schwartz M.** Liver transplantation for hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S268-S276
47 **Kulik L,** Abecassis M. Living donor liver transplantation for hepatocellular carcinoma. Gastroenterology 2004;127: S277-S282
48 Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699
49 **Shetty K,** Timmins K, Brensinger C, Furth EE, Rattan S, Sun W, Rosen M, Soulen M, Shaked A, Reddy KR, Olthoff KM. Liver transplantation for hepatocellular carcinoma validation of present selection criteria in predicting outcome. *Liver Transpl*

2004; **10**: 911-918
50 **Sala M,** Varela M, Bruix J. Selection of candidates with HCC for transplantation in the MELD era. *Liver Transpl* 2004; **10**: S4-S9
51 **Lee JS,** Chu IS, Heo J, Calvisi DF, Sun Z, Roskams T, Durnez A, Demetris AJ, Thorgeirsson SS. Classification and prediction of survival in hepatocellular carcinoma by gene expression profiling. *Hepatology* 2004; **40**: 667-676
52 **Locker J.** A new way to look at liver cancer. *Hepatology* 2004; **40**: 521-523
53 **Graziadei IW,** Sandmueller H, Waldenberger P, Koenigsrainer A, Nachbaur K, Jaschke W, Margreiter R, Vogel W. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. *Liver Transpl* 2003; **9**: 557-563
54 **Cronin DC**, Millis JM, Siegler M. Transplantation of liver grafts from living donors into adults--too much, too soon. *N Engl J Med* 2001; **344**: 1633-1637
55 **Trotter JF,** Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med* 2002; **346**: 1074-1082
56 **Lo CM,** Fan ST, Liu CL, Chan SC, Wong J. The role and limitation of living donor liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2004; **10**: 440-744
57 **Livraghi T,** Meloni F, Morabito A, Vettori C. Multimodal image-guided tailored therapy of early and intermediate hepatocellular carcinoma: long-term survival in the experience of a single radiologic referral center. *Liver Transpl* 2004; **10**: S98-106.
58 **Omata M,** Tateishi R, Yoshida H, Shiina S. Treatment of hepatocellular carcinoma by percutaneous tumor ablation methods: Ethanol injection therapy and radiofrequency ablation. *Gastroenterology* 2004; **127**: S159-166
59 **Head HW,** Dodd GD. Thermal ablation for hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S167-S178
60 **Livraghi T,** Giorgio A, Marin G, Salmi A, de Sio I, Bolondi L, Pompili M, Brunello F, Lazzaroni S, Torzilli G. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. *Radiology* 1995; **197**: 101-108
61 **Lencioni R,** Pinto F, Armillotta N, Bassi AM, Moretti M, Di Giulio M, Marchi S, Uliana M, Della Capanna S, Lencioni M, Bartolozzi C. Long-term results of percutaneous ethanol injection therapy for hepatocellular carcinoma in cirrhosis: a European experience. *Eur Radiol* 1997; **7**: 514-519
62 **Buscarini L,** Buscarini E, Di Stasi M, Vallisa D, Quaretti P, Rocca A. Percutaneous radiofrequency ablation of small hepatocellular carcinoma: long-term results. *Eur Radiol* 2001; **11**: 914-921
63 **Lencioni RA,** Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, Frings H, Laubenberger J, Zuber I, Blum HE, Bartolozzi C. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003; **228**: 235-240
64 **Mulier S,** Mulier P, Ni Y, Miao Y, Dupas B, Marchal G, De Wever I, Michel L. Complications of radiofrequency coagulation of liver tumours. *Br J Surg* 2002; **89**: 1206-1222
65 **Livraghi T,** Solbiati L, Meloni F, Ierace T, Goldberg SN, Gazelle GS. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". *Cancer* 2003; 97: 3027-3035
66 **Lo CM,** Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; **35**: 1164-1171
67 **Llovet JM,** Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359**: 1734-1739
68 **Llovet JM,** Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 2003; **37**: 429-442
69 **Llovet JM,** Bruix J. Unresectable hepatocellular carcinoma: meta-analysis of arterial embolization. *Radiology* 2004; **230**: 300-301
70 **Ren ZG,** Lin ZY, Xia JL, Ye SL, Ma ZC, Ye QH, Qin LX, Wu ZQ, Fan J, Tang ZY. Postoperative adjuvant arterial chemoembolization improves survival of hepatocellular carcinoma patients with risk factors for residual tumor: a retrospective control study. *World J Gastroenterol* 2004; **10**: 2791-2794
71 **Risse JH,** Grünwald F, Kersjes W, Strunk H, Caselmann WH, Palmedo H, Bender H, Biersack HJ. Intraarterial HCC therapy with 1-131-Lipiodol, *Cancer Biother Radiopharm* 2000; **15**: 65-70
72 **Bush DA,** Hillebrand DJ, Slater JM, Slater JD. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase Ⅱ trial. *Gastroenterology* 2004; **127**: S189-193
73 **Fuss M,** Salter BJ, Herman TS, Thomas CR. External beam radiation therapy for hepatocellular carcinoma: potential of intensity-modulated and image-guided radiation therapy. *Gastroenterology* 2004; **127**: S206-217
74 **Geschwind JF,** Salem R, Carr BI, Soulen MC, Thurston KG, Goin KA, Van Buskirk M, Roberts CA, Goin JE. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S194-205
75 **Simonetti RG,** Liberati A, Angiolini C, Pagliaro L, Treatment of hepatocellular carcinoma: a systematic review of randomized controlled trials. *Ann Oncol* 1997; **8**: 117-136
76 **Mathurin P,** Rixe O, Carbonell N, Bernard B, Cluzel P, Bellin MF, Khayat D, Opolon P, Poynard T. Review article: Overview of medical treatments in unresectable hepatocellular carcinoma--an impossible meta-analysis? *Aliment Pharmacol Ther* 1998; **12**: 111-126
77 **Schwartz JD,** Schwartz M, Mandeli J, Sung M. Neoadjuvant and adjuvant therapy for resectable hepatocellular carcinoma: review of the randomised clinical trials. *Lancet Oncol* 2002; **3**: 593-603
78 **Chow PK,** Tai BC, Tan CK, Machin D, Win KM, Johnson PJ, Soo KC. High-dose tamoxifen in the treatment of inoperable hepatocellular carcinoma: A multicenter randomized controlled trial. *Hepatology* 2002; **36**: 1221-1226
79 **Yuen MF,** Poon RT, Lai CL, Fan ST, Lo CM, Wong KW, Wong WM, Wong BC. A randomized placebo-controlled study of long-acting octreotide for the treatment of advanced hepatocellular carcinoma. *Hepatology* 2002; **36**: 687-691
80 **Yang TS,** Lin YC, Chen JS, Wang HM, Wang CH. Phase Ⅱ study of gemcitabine in patients with advanced hepatocellular carcinoma. *Cancer* 2000; **89**: 750-756
81 **Kubicka S,** Rudolph KL, Tietze MK, Lorenz M, Manns M. Phase Ⅱ study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. *Hepatogastroenterology* 2001; **48**: 783-789
82 **Palmieri G,** Biondi E, Morabito A, Rea A, Gravina A, Bianco A. Thymostimulin treatment of hepatocellular carcinoma on liver cirrhosis. *Int J Oncol* 1996; **8**: 827-832
83 **Stefanini GF,** Foschi FG, Castelli E, Marsigli L, Biselli M, Mucci F, Bernardi M, Van Thiel DH, Gasbarrini G. Alpha-1-thymosin and transcatheter arterial chemoembolization in hepatocellular carcinoma patients: a preliminary experience. *Hepatogastroenterology* 1998; **45**: 209-215
84 **Kawata S,** Yamasaki E, Nagase T, Inui Y, Ito N, Matsuda Y, Inada M, Tamura S, Noda S, Imai Y, Matsuzawa Y. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. *Br J Cancer* 2001; **84**: 886-891
85 **Hsu C,** Chen CN, Chen LT, Wu CY, Yang PM, Lai MY, Lee

PH, Cheng AL. Low-dose thalidomide treatment for advanced hepatocellular carcinoma. *Oncology* 2003; **65**: 242-249
86 **Villa E,** Ferretti I, Grottola A, Buttafoco P, Buono MG, Giannini F, Manno M, Bertani H, Dugani A, Manenti F. Hormonal therapy with megestrol in inoperable hepatocellular carcinoma characterized by variant oestrogen receptors. *Br J Cancer* 2001; **84**: 881-885
87 **Mohr L,** Geissler M, Blum HE. Gene therapy for malignant liver disease. *Expert Opin Biol Ther* 2002; **2**: 163-175
88 **Geissler M,** Mohr L, Ali MY, Grimm CF, Ritter M, Blum HE. Immunobiology and gene-based immunotherapy of hepatocellular carcinoma. *Z Gastroenterol* 2003; **41**: 1101-1110
89 **Mohr L,** Yeung A, Aloman C, Wittrup D, Wands JR. Antibody-directed therapy for human hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S225-231
90 **Butterfield LH.** Immunotherapeutic strategies for hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S232-S241
91 **Pei Z,** Chu L, Zou W, Zhang Z, Qiu S, Qi R, Gu J, Qian C, Liu X. An oncolytic adenoviral vector of Smac increases antitumor activity of TRAIL against HCC in human cells and in mice. *Hepatology* 2004; **39**: 1371-1381
92 **Geschwind JF,** Ko YH, Torbenson MS, Magee C, Pedersen PL. Novel therapy for liver cancer: direct intraarterial injection of a potent inhibitor of ATP production. *Cancer Res* 2002; **62**: 3909-3913
93 **Heathcote EJ.** Prevention of hepatitis C virus-related hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S294-S302
94 **Lok AS.** Prevention of hepatitis B virus-related hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S303-S309
95 **Chang MH,** Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, Liang DC, Shau WY, Chen DS. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* 1997; **336**: 1855-1859
96 **Young MD,** Schneider DL, Zuckerman AJ, Du W, Dickson B, Maddrey WC. Adult hepatitis B vaccination using a novel triple antigen recombinant vaccine. *Hepatology* 2001; **34**: 372-376
97 **Chen D,** Weis KF, Chu Q, Erickson C, Endres R, Lively CR, Osorio J, Payne LG. Epidermal powder immunization induces both cytotoxic T-lymphocyte and antibody responses to protein antigens of influenza and hepatitis B viruses. *J Virol* 2001; **75**: 11630-11640
98 **Arntzen CJ.** Pharmaceutical foodstuffs-oral immunization with transgenic plants. *Nat Med* 1998; **4**: 502-503
99 **Kapusta J,** Modelska A, Figlerowicz M, Pniewski T, Letellier M, Lisowa O, Yusibov V, Koprowski H, Plucienniczak A, Legocki AB. A plant-derived edible vaccine against hepatitis B virus. *FASEB J* 1999; **13**: 1796-1799
100 **Richter LJ,** Thanavala Y, Arntzen CJ, Mason HS. Production of hepatitis B surface antigen in transgenic plants for oral immunization. *Nat Biotechnol* 2000; **18**: 1167-1171
101 **Davis HL,** Mancini M, Michel ML, Whalen RG. DNA-mediated immunization to hepatitis B surface antigen-longevity of primary response and effect of boost. *Vaccine* 1996; **14**: 910-915
102 **Prince AM,** Whalen R, Brotman B. Successful nucleic acid based immunization of newborn chimpanzees against hepatitis B virus. *Vaccine* 1997; **15**: 916-919
103 **Choo QL,** Kuo G, Ralston R, Weiner A, Chien D, Van Nest G, Han J, Berger K, Thudium K, Kuo C. Vaccination of chimpanzees against infection by the hepatitis C virus. *Proc Natl Acad Sci USA* 1994; **91**: 1294-1298
104 **Lechmann M,** Murata K, Satoi J, Vergalla J, Baumert TF, Liang TJ. Hepatitis C virus-like particles induce virus-specific humoral and cellular immune responses in mice. *Hepatology* 2001; **34**: 417-423
105 **Lee AY,** Manning WC, Arian CL, Polakos NK, Barajas JL, Ulmer JB, Houghton M, Paliard X. Priming of hepatitis C virus-specific cytotoxic T lymphocytes in mice following portal vein injection of a liver-specific plasmid DNA. *Hepatology* 2000; **31**: 1327-1333
106 **Weiner AJ,** Paliard X, Selby MJ, Medina-Selby A, Coit D, Nguyen S, Kansopon J, Arian CL, Ng P, Tucker J, Lee CT, Polakos NK, Han J, Wong S, Lu HH, Rosenberg S, Brasky KM, Chien D, Kuo G, Houghton M. Intrahepatic genetic inoculation of hepatitis C virus RNA confers cross-protective immunity. *J Virol* 2001; **75**: 7142-7148
107 **Brinster C,** Muguet S, Lone YC, Boucreux D, Renard N, Fournillier A, Lemonnier F, Inchauspé G. Different hepatitis C virus nonstructural protein 3 (Ns3)-DNA-expressing vaccines induce in HLA-A2.1 transgenic mice stable cytotoxic T lymphocytes that target one major epitope. *Hepatology* 2001; **34**: 1206-1217
108 **Forns X,** Payette PJ, Ma X, Satterfield W, Eder G, Mushahwar IK, Govindarajan S, Davis HL, Emerson SU, Purcell RH, Bukh J. Vaccination of chimpanzees with plasmid DNA encoding the hepatitis C virus (HCV) envelope E2 protein modified the infection after challenge with homologous monoclonal HCV. *Hepatology* 2000; **32**: 618-625
109 **Wedemeyer H,** Gagneten S, Davis A, Bartenschlager R, Feinstone S, Rehermann B. Oral immunization with HCV-NS3-transformed Salmonella: induction of HCV-specific CTL in a transgenic mouse model. *Gastroenterology* 2001; **121**: 1158-1166
110 **Jaeckel E,** Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, Pastore G, Dietrich M, Trautwein C, Manns MP. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; **345**: 1452-1457
111 **Gerlach JT,** Diepolder HM, Zachoval R, Gruener NH, Jung MC, Ulsenheimer A, Schraut WW, Schirren CA, Waechtler M, Backmund M, Pape GR. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. *Gastroenterology* 2003; **125**: 80-88
112 **Nomura H,** Sou S, Tanimoto H, Nagahama T, Kimura Y, Hayashi J, Ishibashi H, Kashiwagi S. Short-term interferon-alfa therapy for acute hepatitis C: a randomized controlled trial. *Hepatology* 2004; **39**: 1213-1219
113 **Malik AH,** Lee WM. Chronic hepatitis B virus infection: treatment strategies for the next millennium. *Ann Intern Med* 2001; **132**: 723-731
114 **Torresi J,** Locarnini S. Antiviral chemotherapy for the treatment of hepatitis B virus infections. *Gastroenterology* 2000; **118**: S83-103
115 **Lok AS,** Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000--summary of a workshop. *Gastroenterology*2001; **120**: 1828-1853
116 **Liaw YF,** Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, Tao QM, Shue K, Keene ON, Dixon JS, Gray DF, Sabbat J. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; **351**: 1521-1531
117 **Wands JR.** Prevention of hepatocellular carcinoma. *N Engl J Med* 2004; **351**: 1567-1570
118 **Marcellin P,** Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, Lu ZM, Piratvisuth T, Germanidis G, Yurdaydin C, Diago M, Gurel S, Lai MY, Button P, Pluck N. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004; **351**: 1206-1217
119 **EASL** International Consensus Conference on Hepatitis C. Paris, 26-28, February 1999, Consensus Statement. European Association for the Study of the Liver. *J Hepatol* 1999; **30**: 956-961
120 **Davis GL.** Current therapy for chronic hepatitis C. *Gastroenterology* 2000; **118**: S104-S114
121 **Manns MP,** McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001; **358**: 958-965
122 **Di Bisceglie AM,** Hoofnagle JH. Optimal therapy of hepatitis C. *Hepatology* 2002; 36: S121-S127

123 **Hadziyannis SJ,** Sette H, Jr., Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H, Jr., Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346-355

124 **Yoshida H,** Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, Inoue O, Yano M, Tanaka M, Fujiyama S, Nishiguchi S, Kuroki T, Imazeki F, Yokosuka O, Kinoyama S, Yamada G, Omata M. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann Intern Med* 1999; **131**: 174-181

125 **Nishiguchi S,** Shiomi S, Nakatani S, Takeda T, Fukuda K, Tamori A, Habu D, Tanaka T. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. *Lancet* 2001; **357**: 196-197

126 **Toyoda H,** Kumada T, Nakano S, Takeda I, Sugiyama K, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y, Hayashi K, Honda T. Effect of the dose and duration of interferon-alpha therapy on the incidence of hepatocellular carcinoma in noncirrhotic patients with a nonsustained response to interferon for chronic hepatitis C. *Oncology* 2001; **61**: 134-142

127 **Koike Y, Shiratori Y**, Sato S, Obi S, Teratani T, Imamura M, Hamamura K, Imai Y, Yoshida H, Shiina S, Omata M. Risk factors for recurring hepatocellular carcinoma differ according to infected hepatitis virus-an analysis of 236 consecutive patients with a single lesion. *Hepatology* 2000; **32**: 1216-1223

128 **Muto Y,** Moriwaki H, Ninomiya M, Adachi S, Saito A, Takasaki KT, Tanaka T, Tsurumi K, Okuno M, Tomita E, Nakamura T, Kojima T. Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. Hepatoma Prevention Study Group. *N Engl J Med* 1996; **334**: 1561-1567

129 **Kubo S,** Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Yamazaki O, Shiomi S, Tamori A, Oka H, Igawa S, Kuroki T, Kinoshita H. Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. *Ann Intern Med* 2001; **134**: 963-967

130 **Ikeda K,** Arase Y, Saitoh S, Kobayashi M, Suzuki Y, Suzuki F, Tsubota A, Chayama K, Murashima N, Kumada H. 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* 2000; **32**: 228-232

131 **Takayama T,** Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, Shimada K, Sakamoto M, Hirohashi S, Ohashi Y, Kakizoe T. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomized trial. *Lancet* 2000; **356**: 802-807

132 **Lau WY,** Leung TW, Ho SK, Chan M, Machin D, Lau J, Chan AT, Yeo W, Mok TS, Yu SC, Leung NW, Johnson PJ. Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet* 1999; **353**: 797-801

133 **Boucher E,** Corbinais S, Rolland Y, Bourguet P, Guyader D, Boudjema K, Meunier B, Raoul JL. Adjuvant intra-arterial injection of iodine-131-labeled lipiodol after resection of hepatocellular carcinoma. *Hepatology* 2003; **38**: 1237-1241

Science Editor Wang XL and Guo SY **Language Editor** Elsevier HK