Hepatocellular Carcinoma: An Update

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Hepatocellular carcinoma is one of the most common malignant tumors worldwide. The major etiologies and risk factors for HCC development 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 early hepatocellular carcinoma detection in patients at risk, patient survival has not yet significantly improved during the last three decades. This is in part due to the advanced stage of the disease at the time of diagnosis, and in part due to the limited therapeutic options. These fall into five main categories: 1) surgical interventions, including liver transplantation; 2) percutaneous interventions, including ethanol injection and radiofrequency thermal ablation; 3) transarterial interventions; 4) radiation therapy; and 5) drugs as well as gene and immune therapies. While surgery and percutaneous as well as 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% of patients present with multicentric hepatocellular carcinoma and advanced liver disease or comorbidities that restrict the therapeutic measures to best supportive care. Therefore, early diagnosis, the development of novel systemic therapies for advanced disease and hepatocellular carcinoma prevention are of paramount importance. New technologies, including gene expression profiling and proteomic analyses, should allow to further elucidate the molecular events underlying hepatocellular carcinoma development and to identify novel diagnostic markers as well as therapeutic and preventive targets.

Keywords: Chemotherapy • gene therapy • immune therapy • liver transplantation • percutaneous ethanol injection

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide and has been recently reviewed.1, 2 The incidence of HCC ranges from <10 cases per 100,000 population in North America and Western Europe as well as in Iran, Iraq and India to 50 – 150 cases per 100,000 population in parts of Africa and Asia (Figure 1) where HCC is responsible for a large proportion of cancer deaths.3 However, a rise in the incidence of and mortality from HCC, most likely reflecting the increased prevalence of hepatitis C virus (HCV) infection, has recently been observed in most industrialized countries too.4

The major etiologies of HCC are well-defined (Table 1) and include among the well-known factors an elevated body mass index, especially in men5 as well as diabetes mellitus.6 Some of the steps involved in the molecular pathogenesis of HCC have been elucidated in recent years. As for most types of cancer, hepatocarcinogenesis is a multi-step process involving different genetic alterations that ultimately lead to malignant transformation of the hepatocyte. 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, microscopy) and genetically very
heterogeneous 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 the activation of cellular oncogenes, the inactivation of tumor suppressor genes, possibly in cooperation with genomic instability, including DNA mismatch repair defects and impaired chromosomal segregation, overexpression of growth and angiogenic factors, and telomerase activation. 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 HCC development is liver cirrhosis since 70 – 90% of HCCs develop in a cirrhotic liver. Most HCCs occur after many years of chronic hepatitis that provides the mitogenic and mutagenic environment 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 the etiology of the underlying liver disease. 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. Coexistence of etiologies, e.g., hepatitis B virus (HBV) and HCV infection, HBV infection and aflatoxin B1, HBV/HCV infection and alcohol or diabetes mellitus, HBV infection and liver steatosis, environmental factors, e.g., alcohol as well as diabetes mellitus, obesity and tobacco increase the relative risk of HCC development. Also, occult HBV infection (anti-HBc positive only) carries a significant HCC risk. Interestingly, coffee consumption appears to reduce the HCC risk.

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 — may under certain circumstances play an additional direct role in the molecular pathogenesis of HCC. Finally, aflatoxins have been shown to induce mutations of the p53 tumor suppressor gene, thus pointing to the contribution of an environmental factor to tumor development at the molecular level. Further, 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\textsuperscript{23} and that inhibition of cytotoxic T lymphocyte-induced apoptosis and chronic inflammation by neutralization of the Fas ligand prevents HCC development in this model.\textsuperscript{24} In addition, also in a transgenic mouse model it has been demonstrated that NF-kappa B may be the link between inflammation and HCC development.\textsuperscript{25, 26} Finally, individual polymorphisms of drug metabolizing enzymes, e.g., various cytochrome P450 oxidases, N-acetyltransferases and glutathione-S-transferases, may contribute to the genetic susceptibility to HCC development.\textsuperscript{27}

HCC screening, staging and natural course

HCC screening is routinely done in all individuals at risk for HCC development at six months intervals and includes laboratory tests (liver function tests, tumor markers), imaging analyses, including abdominal sonography, contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) and histopathology.\textsuperscript{28} Apart from alpha fetoprotein (AFP), two additional tumor markers are now commercially available: des-gamma-carboxyprothrombin (DCP) and lens culinaris agglutinin reactive fraction of AFP (AFP-L3).

For staging of HCC, seven systems have been proposed that address the extent and the prognosis of the disease: the “Okuda staging system,”\textsuperscript{31} the “TNM classification” and its modification by the “Union International Centre Cancer” (UICC),\textsuperscript{32} the “Barcelona Clinic Liver Cancer” (BCLC) classification,\textsuperscript{33} the “Cancer of the Liver Italian Program” (CLIP) score,\textsuperscript{34} the “Japan Integrated Staging” (JIS) score,\textsuperscript{35} the “Groupe d’Etude de Traitement du Carcinoma Hepatocellulaire” (GRETCH) score\textsuperscript{36} and the “Chinese University Prognostic Index” (CUPI). The Okuda staging system is very effective for identification of a subgroup of patients (Okuda III) with a very poor prognosis who should be treated with best supportive care (BSC) only. The BCLC classification appears especially useful for the selection of treatment options but has not been independently validated. The CLIP score was shown to be superior to the Okuda staging system but has not been systematically assessed in patients undergoing resection or liver transplantation (LTx). While a recent study indicated that the new prognostic JIS score is superior to the CLIP score,\textsuperscript{37} a comparison of the staging systems in an American cohort revealed that the BCLC had the best independent predictive power.\textsuperscript{38}

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 ‘O’ or Okuda stage I the median survival is in the range of 23 – 69 months, while in patients with CLIP score 3 – 5 or Okuda stage III, the median survival is only 1 – 14 months.\textsuperscript{38} The staging system is clinically most important for the appropriate choice of the therapeutic strategy for individual patients. Cirrhotic patients who developed HCC over the last five years of surveillance, have survived longer than previously, due to improved management of the tumor and of the complications of cirrhosis.\textsuperscript{39} Importantly, however, in a population-based study in the US underutilization of potentially curative therapies even among patients with favourable HCC features is a problem that needs to be addressed.\textsuperscript{40}

Treatment of HCC

Therapies for HCC can be divided into five categories: Surgical interventions (tumor resection and LTx), percutaneous interventions (ethanol injection, radiofrequency thermal ablation), transarterial interventions (embolization, chemoperfusion, or chemoembolization), radiation therapy and chemotherapy, including gene- and immune-therapy (Figure 2). Potentially curative therapies are tumor resection, LTx, and percutaneous interventions that can result in complete responses and improved survival in a high proportion of patients. In selected cases, transarterial interventions results in palliation with good response rates and improved survival. Drugs as well as conventional radiotherapy have no proven efficacy to date.

To date, surgical, percutaneous and transarterial interventions have not been compared in randomized controlled trials. Tumor resection and LTx in selected patient populations, result in 5-year survival rates of 60 – 70%, with LTx being the best treatment for patients with single lesions and advanced liver disease, e.g., decompensated cirrhosis, or mult centric small tumours. Percutaneous interventions, again in selected patient populations, result in 5-year survival rates of 40 – 50%. In the following section, the different therapeutic options as well as primary and
secondary HCC prevention will be discussed in detail.

**Surgical interventions**

**Resection**

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

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 <10 mmHg, no esophageal varices, no splenomegaly, platelet counts >100×10⁹/L) and one asymptomatic HCC lesion only, 5-year survival rates of 70% can be achieved. By comparison, in patients with clinically-relevant portal hypertension, 5-year survival rates are about 50% only; in those with portal hypertension and evidence of impaired liver function, 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 at five years is a major clinical problem. The risk of recurrence is especially high in patients with microvascular invasion and/or additional tumor nodules. Therefore, strategies aimed at secondary HCC prevention are of paramount importance (see below).

**Liver transplantation**

LTx is in principle, the optimal therapeutic option for HCCs because it simultaneously removes the tumour and the underlying cirrhosis, including the risk of HCC recurrence. While broad selection criteria applied previously led to poor results with recurrence rates of about 50% and a 5-year survival rate of <40%, the current criteria for LTx in patients with HCC (one lesion <5 cm in diameter or maximum three lesions <3 cm in diameter) result in a 5-year survival rate of ≥70% and a recurrence rate of <15%. Possibly, these criteria can be extended in the future, depending on more experience 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.

Clinically, it is most important to shorten the waiting time for LTx to <6 months. This is difficult to achieve with cadaveric LTx given the shortage of donors. With a waiting time of >12 months in
some Western countries, the drop-out rate of patients is 20 – 50%. To bridge the time to LTx and to prevent tumor progression, neoadjuvant treatment, e.g., percutaneous and transarterial interventions may lead to an improved outcome (see below). While marginal livers, domino donors, and split LTx had no major impact, living donor LTx has been shown to be an alternative to cadaveric LTx. Around 3,000 interventions have been done worldwide. However, living donor LTx is a complex procedure that is associated with a morbidity of 20 – 40% and a donor mortality of 0.3 – 0.5%. Therefore, a very careful selection of patients and donors, including the consideration of ethical, societal and legal issues are central to the successful implementation of living donor LTx for the treatment of patients with HCCs.

Percutaneous interventions

Percutaneous interventions are the best options for small unresectable HCCs. Tumor ablations can be achieved chemically by percutaneous ethanol injection (PEI) or acetic acid injection (PAI) or thermally by radiofrequency thermal ablation (RFA), high frequency induced thermotherapy (HiTT), laser-induced thermotherapy (LiTT), or cryoablation. Apart from percutaneous interventions, these techniques can also be applied laparoscopically or after laparotomy.

Percutaneous ethanol injection.

PEI is the technique most widely used. It is safe, easy to perform, inexpensive and achieves complete tumor response rates of 90 – 100% in HCCs smaller than two cm in diameter, 70% in HCCs of three cm in diameter and 50% in HCCs of five cm in diameter. Patients with liver cirrhosis Child A with complete responses can achieve a 5-year survival rate of ≥50%. Therefore, PEI is the procedure of choice for patients with a single HCC lesion <5 cm in diameter or with up to three lesions <3 cm in diameter. Survival is predicted by the initial response to PEI. However, a recent comparative study demonstrated that LTx is superior to PEI.

Radiofrequency thermal ablation

RFA is an alternative to PEI. Several devices are available that can be applied percutaneously, laparoscopically, or during laparotomy. The efficacy of RFA is similar to PEI but generally requires only a single session. While more expensive than PEI, RFA offers a better local tumor control and has the potential advantage of allowing the ablation of tumors >5 cm, especially with newer generation devices. However, 5-year survival rates after complete response to RFA are currently, similar to PEI — around 30 – 40% — depending on the Child stage of the underlying liver cirrhosis. In a review of 3,670 patients treated by RFA, the mortality rate was 0 – 5% and the complication rate was 8 – 9%. Predictors of treatment response are tumour size and morphology (well-encapsulated vs. invasive). While safe and in case of a complete response highly effective with a prolonged survival, RFA is associated with a high risk of tumor persistence in the targeted nodule. Therefore, in a curative setting, RFA should not be considered as an independent HCC therapy but it should be considered as a bridging strategy for other therapeutic interventions, including LTx.

Another non-invasive thermal HCC ablation is based on MRI-guided high-intensity focused ultrasound (HIFU). While there is relatively little experience with this technique to date, this method may eventually be proven clinically useful, possibly in combination with a transarterial intervention (see below).

Taken together, percutaneous HCC ablation by PEI and/or RFA is an effective treatment for patients with HCCs. It prolongs tumor-free and overall survival, especially if surgery is not feasible. This strategy is now being evaluated also for the treatment of liver metastases.

Transarterial interventions

Transarterial embolization (TAE), chemoperfusion (TAC) and chemoembolization (TACE) are the most widely used treatments for HCCs that are unresectable or cannot be effectively treated by percutaneous interventions. Embolization agents may be administered alone (embolization) or after selective intra-arterial chemotherapy (generally doxorubicin, mitomycin or cisplatin) mixed with lipiodol (chemoembolization). TAE and TACE result in partial responses in 15 – 55% of patients, delay tumour progression and vascular invasion and result in a survival benefit compared with conservative management. The most important aspect is the selection of patients, i.e., patients should have preserved liver function (Child A) and asymptomatic multinodular tumours without vascular invasion or extrahepatic spread. In a prospective study on 8,510 patients the 5- and 7-year survivals were 26% and 16%,
respectively; the severity of the underlying liver disease, tumor stage, and AFP level being independent prognostic factors. In patients with advanced liver disease (Child B or C), however, treatment-induced liver failure may offset the anti-tumor effect or survival benefit of the intervention.

In a randomized controlled clinical the combination of TACE and PEI improved the survival of patients with HCC Okuda stage I better than TACE alone. Further, postoperative adjuvant TACE may improve survival in patients with risk factors for residual tumor.

Radiation therapy

While radiation therapy has played a minor role in the primary treatment of HCC to date, selective intra-arterial injection of 131 iodine-labeled lipiodol has been performed in some patients 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. These strategies will certainly be further explored in clinical studies and may become a treatment option in the future.

Drugs

A number of systemic chemotherapies, hormonal and other drugs (Table 2) have been evaluated in clinical trials. While most chemotherapeutic agents, tamoxifen, octreotide, and interferon have not been shown to be effective in randomized controlled clinical trials, there are a number of substances that may deserve further clinical evaluation, e.g., gemcitabine, thymophsin, α-1-thymosin, pravastatin, thalidomide, and megestrol acetate, several antiangiogenic small molecules, e.g., erlotinib, gefitinib, and sorafenib as well as antiangiogenic monoclonal antibodies, e.g., bevacizumab or cetuximab, Cox-2 inhibitors in combination with capreptabine, pamidronate etc. Furthermore, in an animal model, troglitazone resulted in an impressive reduction of HCC growth. To date, however, none of these drugs can be recommended outside of clinical studies.

Experimental strategies

In view of the limited therapeutic options for advanced HCCs, a number of experimental strategies are being evaluated, including gene- and immune-therapies based on suicide, cytokine and antiangiogenic genes or DNA vaccination with tumor-specific genes, as well as novel drugs, e.g., 3-bromopyruvate.

HCC prevention

HCC prevention falls into two categories. Primary prevention is aimed at the interference with HCC development at four stages (Figure 3). 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 the 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. For the prevention of HCV infection, however, there is no effective vaccine available to date. Stage 2: Interventions at this step are aimed at the early treatment of acute hepatitis, thereby blocking their transition into a chronic liver disease. 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 for HCC development. 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.

Figure 3. Primary HCC prevention.
and HCC. 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. Finally, LTx in patients with liver cirrhosis before development of HCC is a highly effective preventive measure.

After successful resection of HCC or non-surgical ablation, the recurrence, in most cases with cirrhotic liver, is the major limitation of the life expectancy of these patients. The probability of recurrence is about 50% within three years after successful treatment. Strategies to prevent HCC recurrence are therefore central to the improvement of survival of HCC patients after initial cure. Apart from LTx after successful resection, the strategies explored to date include the administration of polypropenoic acid, an acyclic retinoid, of interferon alpha and of interferon beta. Moreover, adoptive immunotherapy and intra-arterial injection of iodine-labeled lipiodol has been evaluated in clinical studies. Furthermore, postoperative adjuvant TACE may also improve survival in patients with risk factors for residual tumor. All these interventions have resulted in lower HCC recurrence rates. These findings have to be confirmed, however, in larger randomized controlled trials demonstrating a clear clinical benefit before secondary prevention with one of the strategies mentioned above should enter the 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 five main categories: 1) surgical interventions, including tumor resection and LTx; 2) percutaneous interventions, including PEI and RFA; 3) transarterial interventions, including TAC, TAE and TACE, 4) radiation therapy and 5) drugs as well as gene- and immune-therapies. While surgery and percutaneous as well as transarterial interventions are effective in patients with limited disease (up to three lesions <3 cm in diameter or one lesion ≤5 cm in diameter) and compensated underlying liver disease (cirrhosis Child A), at the time of diagnosis >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 from HCC, therefore, 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 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.

References


Table 2. Drugs evaluated or currently in clinical trials to treat patients with HCC.

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<tr>
<th>Chemotherapeutic agents</th>
<th>5-Fluorouracil</th>
<th>Capecitabine</th>
<th>Gemcitabine</th>
<th>Doxorubicin</th>
<th>Epirubicin</th>
<th>Etoposide</th>
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<td>Hormones or anti-hormones</td>
<td>Megestrol acetate</td>
<td>Tamoxifen</td>
<td>Ocreotide</td>
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<td>Angiogenesis inhibitors</td>
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<td>Cetuximab</td>
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<td>Others</td>
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<td>Troglitazone</td>
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Hepatocellular carcinoma


71 Camma C, Di Marco V, Orlando A, Sandonato L, Casaril A, Parisi P, et al. Treatment of hepatocellular carcinoma...


