Hepatocellular Cancer

DO Whittle[1], L Roberts[2]

Epidemiology

Hepatocellular cancer (HCC) is the fifth most common cancer worldwide and the third most frequent cause of death from cancer (1).

The highest incidence reports of HCC are in Asia and sub-Saharan Africa (3). Southern Europe also has a high incidence. According to the International Agency for Research on Cancer (IARC) in 2002, worldwide incidence ratios were 15.8 cases per 100 000 per year for men and 5.8 cases per 100 000 per year for women (9). In Jamaica, according to the IARC, in 2002 the incidence of liver cancers for males was 4.1 and females 3.3 per 100 000 per year. The highest incidence regions in Asia and Africa have a high prevalence of chronic hepatitis B as well as significant exposure to dietary aflatoxins (9). Combinations of risk factors that are important in the epidemiology of HCC include co-infection of hepatitis B and hepatitis C, alcohol use and other causes of cirrhosis of the liver. The risk of HCC increases with age. There is a significant effect of gender on the risk of development of HCC. The worldwide male to female incidence ratio is 2.7:1.

Risk Factors

Risk factors for primary HCC are chronic hepatitis B, C and indeed cirrhosis of any cause such as alcoholic liver disease, Non-alcoholic Fatty Liver Disease (NAFLD) and haemochromatosis (3). Environmental toxins, namely aflatoxin found in peanuts, have been associated with HCC (4).

Chronic Hepatitis B

There are 350 – 400 million chronic HBV carriers worldwide (9). In low prevalence countries, sexual contact is the predominant mode of transmission, while in high prevalence countries, most HBV infections are contracted perinatally or in early childhood. A quarter of individuals with chronic hepatitis B infection develop progressive liver disease and up to 20% of these patients develop cirrhosis (9). The risk of HCC varies from 2% to 10% per year in patients with cirrhosis. Vaccination of infants and at risk individuals decreases the prevalence of chronic hepatitis B infection and the incidence of HCC.

From: [1]Department of Medicine, The University of the West Indies, Kingston 7, Jamaica, [2]Mayo Clinic, Division of Gastroenterology and Hepatology, Rochester, Minnesota, USA.

Correspondence: Dr DO Whittle, Department of Medicine, The University of the West Indies, Kingston 7, Jamaica, West Indies. Email: dowhittlejr@yahoo.com

Chronic Hepatitis C

About 170 million people worldwide are infected with the hepatitis C virus. Those at highest risk for acquiring hepatitis C are recipients of contaminated blood transfusions, unsanitary health practices with contaminated needles and IV drug users. Chronic hepatitis C is a slowly progressive disease. Persistently high ALT levels and co-infection with hepatitis B are significant predictors for development of HCC. After surgical resection, the presence of active hepatitis and hepatitis C are risk factors for tumour recurrence. Prior treatment of hepatitis C with interferon or interferon and ribavirin with persistence of a sustained viral response is protective against the initial development of HCC or recurrence after surgical resection.

Dietary Aflatoxin Exposure

Aflatoxin is a mycotoxin produced by the fungus Aspergillus. Aspergillus is widespread in nature occurring in soil and decaying vegetation, in conditions of high moisture and temperatures. There are many types of aflatoxins with aflatoxin B1 being most carcinogenic. Aflatoxins are metabolized in the liver by the cytochrome p450 and glutathione S-transferase enzyme systems. Aflatoxin B1 is a procarcinogen that is converted in the liver to a mutagenic metabolite. Exposure to aflatoxin also predisposes to mutations in p53 gene, an event that contributes to the pathogenesis of HCC. The carcinogenic effect of aflatoxin is increased by infections with chronic hepatitis B and C.

Pathogenesis of HCC

Oncogene activation and tumour suppression inactivation play key roles in carcinogenesis of HCC. The mechanisms of liver carcinonogenesis are under intense investigation. In cirrhotic livers, macro-regenerative nodules with foci of hepatocyte dysplasia have been identified as precancerous lesions. Hepatocellular cancer (HCC) occurs in multiple genetic and environmental contexts.

Multiple mechanisms appear to contribute to hepatitis B-induced hepatic carcinogenesis. Although persistent hepatitis with regenerative hepatocellular turnover and the eventual development of cirrhosis is presumed to play a significant role in HBV-induced carcinogenesis, a significant percentage of HBV-induced HCC occur in the absence of liver cirrhosis. This suggests that separate carcinogenic mechanisms exist that can drive carcinogenesis in the absence of cirrhosis with respect to HBV. Hepatitis B is a small DNA virus that integrates into the genome in almost all patients with chronic hepatitis. This integration is thought to lead to carcinogenesis through a number of pathogenic pathways:

a) Generalized genomic instability leads to focal deletions and translocations
b) HBV-induced modalities of gene transcrip-tional mistakes
c) Oncogenic effects of HBV proteins such as the X and pre-S proteins
d) HBV proteins cause inhibition of tumour suppressor genes

In patients with chronic hepatitis C infection, persistent liver damage results in repeated cycles of liver injury and regeneration that result in premature cellular senescence of the liver and the development of genetic aberrations. Within the context of a highly genotoxic environment with increased reactive oxygen species and inflammatory cytokines, additional genetic aberrations cause the initiation of the malignancy (10). Subsequent secondary changes in the tumour micro-environment contribute to the neoangiogenesis, invasiveness and metastases that are typical in HCC.

Clinical Features

Most patients with HCC are asymptomatic early in the disease. Patients with early stage disease are usually found during surveillance of patients at risk for HCC. Decompensation of liver disease, in patients with cirrhosis, manifested by ascites, spontaneous bacterial peritonitis, variceal bleeding and encephalopathy may herald the onset of HCC particularly when a hepatic or portal vein branch is invaded. Patients with advanced disease may present with an abdominal mass, obstructive jaundice, an acute abdomen due to intratumoral haemorrhage or intraperitoneal rupture, paraneoplastic phenomena such as diarrhoea, fever of unknown origin, metastatic disease and constitutional symptoms.

Tumoral effects include anorexia, weight loss, malaise and painful hepatomegaly. Spontaneous rupture of the cancer into liver parenchyma or peritoneum can present as acute abdomen. Fever of unknown origin is an unusual presentation and is associated with leukocytosis.

Hepatocellular cancer may result in decompensation of cirrhosis by vascular invasion of portal vein or its branches, worsens portal hypertension and hence results in ascites and variceal bleeding. This effect is also caused by infiltration at the level of the sinusoids which worsens hepatic function resulting in hyperbilirubinaemia, coagulopathy and encephalopathy.

Paraneoplastic phenomena include hypercalcaemia due to parathyroid hormone-like hormone, hypoglycaemia due to insulin-like growth factors, thrombophlebitis migrans and erythrocytosis due to erythropoietin produced by the tumour.

Laboratory features include elevated bilirubin, alkaline phosphatase and transaminases with prolongation of the prothrombin time and low albumin levels. Alpha-fetoprotein levels are elevated in 75% of cases, and a value greater than 400 ng/ml has 95% specificity for hepatocellular cancers (5).

Staging and Screening of HCC

Staging is done using the TNM staging system but some authorities have incorporated the state of the liver as well into the CLIP (Cancer of the Liver Italy Programme) staging system (6). The Okuda System for staging uses tumour size, serum albumin, presence of ascites and bilirubin levels into stages 1, 2 and 3. The Barcelona Clinic Liver Cancer (BCLC) staging system consists of four stages based on the extent of the primary lesion, performance status, presence of constitutional symptoms, vascular invasion, extrahepatic spread and the Okuda system.

Patients at risk for HCC should be listed in a surveillance programme. Patients should be screened at 6 –12 monthly intervals with abdominal ultrasound and alpha-fetoproteins. Other serum tumour markers include Des-gamma-carboxy prothrombin, serum alpha-L-fucosiade activity (7). These latter markers have not shown any superior efficacy over alpha-fetoproteins.

Diagnosis

Imaging the liver with ultrasound, computed tomography or magnetic resonance imaging often identifies and can fairly predict the diagnosis. Histological confirmation from a biopsy is only occasionally required. There are concerns about possible seeding of the tumour in the needle tract, which has the potential of worsening the stage of the cancer and thus exclude a patient from transplantation or surgery. According to the American Association for the Study of Liver Diseases (AASLD) guidelines, a mass found incidentally or on screening in the setting of a patient with known hepatitis B or cirrhosis of other aetiology is likely to be HCC. The subsequent tests to establish the diagnosis depends on the size of the lesion.

Patients with:

– Lesions < 1 cm should have ultrasound 3 – 6 monthly. If no growth over 2 years, one can revert to routine screening.
– Lesions 1 – 2 cm on ultrasound, in cirrhotic patients, should have 2 dynamic studies, contrast CT, ultrasound or contrast MRI. If features are typical of HCC (hypervascularity with washout in venous phase) then the lesion should be treated as HCC. If findings are not typical then the lesion should be biopsied.
– In lesions > 2 cm, with typical features of HCC on one dynamic imaging technique, biopsy is not necessary. If the lesion is atypical in a non-cirrhotic patient, then the lesion should be biopsied.

Treatment

Patients with early disease should be evaluated for surgical resection. Ideal candidates are patients with a solitary lesion < 5 cm, no evidence of vasculature invasion, no portal hypertension and well-preserved liver functions. Patients who are

good candidates for resection should have Child-Pugh Class A or a Model for End-Stage Liver Disease (MELD) score < 7. Intrahepatic recurrence of HCC after an apparent curative resection is not uncommon, since the neoplastic potential of the non-resected liver remains unchanged. A wedged hepatic venous pressure gradient above 10 mmHg is considered to be a contraindication for resection or platelet count less 100 000 /fl or the presence of varices on endoscopy.

Orthotopic liver transplantation (OLT) is a suitable option for patients with early disease who have severe liver dysfunction and are not surgical candidates. Orthotopic liver transplantation offers several advantages over partial hepatectomy: it can be employed for patients with all stages of liver disease and it will address the cancer, the neoplastic potential of the liver and the liver disease itself. Best outcomes, however, requires patients not to demonstrate any local or regional metastases and the tumour must be less than 5 cm if solitary and 3 cm if up to 3 lesions [the Milano Criteria] (8). The most important limitation of OLT is an increasing organ shortage. In addition, the long waiting period for a donor organ often allows a small tumour to become larger or even metastatic. In fact, the dropout rate in a 6-month period may be as high as 25%. Hence many centres in the USA treat these lesions prior to OLT to prevent tumour growth and metastasis.

In patients who meet the criteria for both resection and OLT, best outcomes are obtained from OLT because of the high rate of recurrence following resection. However, surgical resection may be preferred if effective secondary chemoprevention therapies are discovered as it would avoid the need for long term immunosuppression. Many patients however do not fit these strict criteria hence other methods have been employed including locoregional therapies such as radiofrequency ablation, percutaneous ethanol ablation, transarterial chemo-embolization, radiation and systemic chemotherapy.

Percutaneous alcohol injection

Percutaneous alcohol injection (PEI) is an option for small localized HCC. It is a relatively simple technique and of low cost and can be used in advanced cirrhosis. Most suitable cases are HCC < 3 cm and fewer than 3 nodules. The destruction of tumour cells by injection of absolute alcohol is probably due to cellular dehydration, coagulation necrosis and vascular thrombosis followed by ischaemia. The extent of necrosis depends on the tumour size. A small lesion may require only one treatment while larger lesions may require several treatments. Injection is done under CT or US guidance. Follow-up should be done using spiral CT scans; PEI can be repeated if recurrence occurs. Complications include abdominal pain due to leakage of alcohol into the peritoneal space and low grade fever with tumour necrosis. Contraindications include massive ascites, coagulopathy and obstructive jaundice.

Radiofrequency Ablation

Radiofrequency ablation (RFA) destroys cancer tissues by thermal energy generated with an alternating electric current generator that operates in the radiofrequency range 200 – 1200 kHz. A needle electrode is percutaneously guided into the centre of the tumour. Radiofrequency ablation is not effective for lesions adjacent to large veins in the liver and segment 8 of the liver. Spiral CT is used to assess tumour necrosis and can be repeated for new lesions. Concerns have been raised *re* needle tract seeding. Studies have demonstrated superiority of RFA over PEI.

Transcatheter arterial chemo-embolization

Transcatheter arterial chemo-embolization (TACE) uses angiography to selectively embolize the arterial supply of HCC. Access is by the common femoral artery and doxorubicin or cisplatin in a suspension with lipiodol is injected into a feeding artery of the tumour. It causes selective ischaemia and has chemotherapeutic effects on the HCC. There is minimal damage on normal liver tissue due to the dual blood supply. Complications of TACE include contrast allergy, contrast nephropathy, bleeding, pseudoaneurysm, hepatic abscess, fever and abdominal pain. Advanced Child-Pugh C cirrhosis is a relative contraindication for TACE because of the high risk of fatal complications such as liver failure. Others include hepatic encephalopathy, biliary obstruction and portal vein obstruction. Tumour lysis syndrome occurs often because the blood supply to the tumour is abruptly discontinued with ensuing necrosis of the tumour. Transcatheter arterial chemoembolization is often used as a bridge to liver transplantation as it avoids the risk of needle track seeding. It is contraindicated in the presence of portal vein or hepatic vein thrombosis.

Transcatheter arterial radio-embolization

Transcatheter arterial radio-embolization (TARE) is similar to TACE in that radiolabelled particles are infused into the hepatic artery and flow into the vascular bed of HCC, with sparing of normal liver tissue. TARE is available in two variants – Yttrium 90 impregnated glass microspheres (Theraspheres) and as resin-based microspheres. Theraspheres have high specificity and hence a small mass of beads is infused into the tumour vasculature which does not occlude blood flow hence reduces the risk of tumour lysis syndrome that occurs in TACE. Hence TARE can be administered to patients with HCC and portal vein thrombosis, where TACE is contraindicated.

A planning angiogram is performed prior to Theraspheres administration to assess risk of lung radiation due to shunts. A high lung shunt would lead to lung radiation injury from the radiolabelled microspheres and is a contraindication to the therapy. Theraspheres administration has been shown to downstage HCC to allow resection, RFA and as a bridge to transplantation.

Systemic Therapy

Traditionally, HCC was considered chemotherapy resistant cancer. However, systemic therapies are used as adjuvant therapy in combination with surgery and locoregional therapies and should be used in clinical trials only. Most of these therapies have been shown to be of little efficacy. The Sharp Trial has revealed survival benefits in patients with advanced HCC with the use of the multitargeted tyrosine kinase inhibitor sorafenib (11). Sorafenib affects tumour cells angiogenesis and proliferation by interactions with receptor RAF kinase and vascular endothelial factor receptor. The multicentred European phase 3 Sharp Trial randomly assigned patients with advanced HCC and Child-Pugh A which were inoperable to sorafenib 400 mg twice daily to placebo. Preliminary results revealed that the primary endpoint, overall survival, was greatly reduced in the sorafenib group compared to placebo (10.7 *versus* 7.9 months). Treatment was well tolerated with manageable side effects. The most significant side effects were diarrhoea and hand-foot syndrome. There were no differences in liver dysfunction and bleeding.

Prevention

The prevention of HCC aims at preventing cirrhosis: avoiding toxins *eg* alcohol and the infectious causes of cirrhosis. All pregnant women should be tested for hepatitis B and Hepatitis B Immune Globulin (HBIG) should be administered within 12 hours of birth to neonates born to HBsAg – positive mothers. Hepatitis B vaccination should be instituted immediately after birth. At one year of age, follow-up should be done to ascertain seroconversion. Treatment of high risk neonates with HBIG plus vaccination reduces the risk of chronic infection and HCC.

Conclusion

Liver cancers remain aggressive tumours that occur in the setting of chronic liver disease and cirrhosis. Most patients are not candidates for curative treatment. To prevent this cancer, efforts should be made to avoid preventable causes of hepatic cirrhosis.

References

1. Parkin DM. Global cancer statistics in the year 2000. Lancet Oncol 2001; **2:** 533–43.
2. Wong R, Corley DA. Racial and ethnic variations in hepatocellular carcinoma incidence within the United States. Am J Med 2008; **121:** 525–31.
3. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology 2004; **127:** 1372–80.
4. Bressac B, Kew M, Wands J, Ozturk M. Selective G to T mutations of p53 gene in hepatocellular carcinoma from southern Africa. Nature 1991; **350:** 429–31.
5. Peng SY, Chen WJ, Lai PL, Jeng YM, Sheu JC, Hsu HC. High alpha-fetoprotein level correlates with high stage, early recurrence and poor prognosis of hepatocellular carcinoma: significance of hepatitis virus infection, age, p53 and beta-catenin mutations. Int J Cancer 2004; **112:** 44–50.
6. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology 1998; **28:** 751–5.
7. Takahashi H, Saibara T, Iwamura S, Tomita A, Maeda T, Onishi S et al. Serum alpha-L-fucosidase activity and tumor size in hepatocellular carcinoma. Hepatology 1994; **19:** 1414–7.
8. Hemming AW, Cattral MS, Reed AI, Van Der Werf WJ, Greig PD, Howard RJ. Liver transplantation for hepatocellular carcinoma. Ann Surg 2001; **233:** 652–9.
9. Cancer Incidence in five continents: IARC scientific publications volume VIII (No. 155), Parkin, DM (ed), Lyon: IARC Press 2002.
10. Huang H, Shiffman ML, Friedman S, Venkatesh R, Bzowej N, Abar OT et al. "A 7 Gene Signature Identifies the risk of Developing Cirrhosis in Patients with Chronic Hepatitis C" Hepatology. 2007; **46:** 297–06
11. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; **359:** 378–90.