Forum

Overview: Hepatocellular carcinoma - the future starts now

Jacob George and Monica Robotin

Abstract

While hepatocellular cancer remains relatively uncommon in Australia, incidence rates have been progressively rising over the last few decades. Hepatocellular cancer has well-defined risk factors, some of them amenable to modulation or eradication. Currently, chronic hepatitis B or C infection accounts for approximately 80% of all primary liver cancers, but as hepatitis B vaccination will lead to fewer hepatitis B-related cancers, more cases will be due to hepatitis C or non-alcoholic fatty liver disease. Cancer control strategies are contingent upon the ability to prevent liver disease progression to cirrhosis and the eradication or suppression of viral replication; the extent to which screening improves disease-specific or all-cause mortality remains unclear. Our understanding of hepatocellular cancer biology and of viral hepatitis has dramatically increased in recent years, as a result of cross-disciplinary collaborations between clinicians, epidemiologists, public health practitioners and basic scientists. Hepatocellular cancer responds poorly to conventional chemotherapy, but the advent of new and more effective therapies –particularly biological agents that specifically target the molecular basis of neoplastic growth and metastasis – is expected to make a significant impact in coming years. We hope that this issue of *Cancer Forum* will convince the reader that we are now at the threshold of a better future for this previously untreatable malignancy.

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Epidemiology of primary liver cancer

Noore Alam, Monica Robotin and Deborah Baker

Abstract

Cancer of the liver is a significant cause of morbidity and mortality worldwide. Globally, 625,000 cases of liver cancer were reported in 2002. The worldwide distribution of liver cancer is characterised by a great geographic variability, with age-standardised incidence rates ranging from more than 30 cases per 100,000 population in eastern Asia and parts of Africa, to fewer than five per 100,000 in the Americas and in Northern Europe. Much of this variability in the distribution of the disease is related to the global distribution and the natural history of infection with hepatitis B and C viruses. In Australia, both the incidence of and mortality from liver cancer have been progressively rising since the mid-1980s. The age standardised incidence rates for liver cancer are highest in some overseas-born Australians, especially among those born in hepatitis B and C endemic countries. The incidence of primary liver cancer in Australia is projected to continue to rise over the next two decades, as a result of a large reservoir of asymptomatic infections with chronic viral hepatitis, immigration from countries of high hepatitis B virus prevalence and the slow disease progression from chronic hepatitis B virus infection to liver cancer. Public health strategies for targeted interventions for the prevention, treatment and control of chronic viral hepatitis infection may effectively reduce the burden of liver cancer globally, as well as in Australia.

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Liver carcinogenesis

Janina Tirnitz-Parker and John Olynyk

Abstract

Hepatocellular carcinoma occurs most commonly in the setting of cirrhosis, where the annual rate of cancer development approximates 3-7%. Most cases arise in the setting of impaired liver regeneration combined with chronic inflammation and fibrosis. Liver progenitor cells play an important role in cell renewal processes in the liver in the setting of chronic injury and have recently emerged as potential candidates in the carcinogenic pathway. There are two main hypotheses which have been proposed to explain hepatocellular carcinogenesis, namely the de-differentiation and the maturation arrest hypotheses. Understanding the carcinogenic pathways and the role of liver progenitor cells will provide greater understanding and novel approaches to preventative strategies.

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Trends in chronic viral hepatitis: notifications, treatment uptake and advanced disease burden

Hla-Hla Thein and Gregory J Dore

Abstract

Since the introduction of mandatory notification in the early 1990s, around 110,000 and 260,000 cases of hepatitis B and hepatitis C respectively, have been reported through public health surveillance mechanisms in Australia. The number of hepatitis B notifications is likely to be a considerable underestimation of the number of people living with chronic hepatitis B. Over the period 1998-2008, a small decrease in hepatitis B notifications (around 10%) and a more marked decrease in hepatitis C notifications (around 40%) has occurred, with the latter related to reductions in heroin supply. Rates of antiviral therapy remain low for both chronic hepatitis B (<3%) and chronic hepatitis C (<2%). Incidence of hepatocellular carcinoma has increased over the period 1990-2002, largely due to increasing contributions of hepatitis B virus and hepatitis C virus related hepatocellular carcinoma. Further increases in hepatocellular carcinoma incidence are projected, particularly if antiviral therapy uptake remains low. A combination of enhanced access to treatment programs and increased hepatocellular carcinoma screening among high risk people with chronic hepatitis B and chronic hepatitis C is required to limit the emerging epidemic of chronic viral hepatitis related hepatocellular carcinoma.

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Risk of hepatocellular carcinoma in chronic viral hepatitis

Lara J Kane and Graeme A Macdonald

Abstract

Chronic viral hepatitis B and C infections are the diseases associated with the highest risk for developing hepatocellular carcinoma. These infections are prevalent worldwide. Many factors modulate the risk of developing hepatocellular carcinoma in chronic viral hepatitis, such that the assessment of an individual patient's risk is a complex consideration. The presence of cirrhosis is the most important risk factor for the development of hepatocellular carcinoma in both hepatitis B and C. Thus, one of the major mechanisms for hepatocarcinogenesis in these infections is mediated in some way through chronic liver injury. In addition, there is evidence to support a direct oncogenic effect of both HBV and HCV, although the evidence is weaker for HCV. Other risk factors for hepatocellular carcinoma in chronic viral hepatitis include: geographical location; whether in a high or low prevalence area; host factors, particularly sex and age; and specific viral factors. In chronic hepatitis B without cirrhosis the risk of hepatocellular carcinoma is 0.5%-0.8% per annum, increasing to 1.4-2.5% in cirrhotic patients. In chronic hepatitis C with cirrhosis the risk is 1.4-2.5% per annum, while in Australia, patients with hepatitis C rarely develop hepatocellular carcinoma in the absence of cirrhosis.

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Anti-viral medication to prevent HCC development: where are we now?

Nadia Warner, Stephen Locarnini and Tin Nguyen

Abstract

Hepatitis B virus was the first human virus unequivocally associated with malignancy. Long-term persistent infection with hepatitis B virus can result in the development of chronic liver disease, cirrhosis and hepatocellular carcinoma. Not surprising then, the main goal of antiviral therapy for chronic hepatitis B is to prevent the development of these life-threatening complications. The clinical trial treatment data now indicates that these goals are beginning to be achieved. Unfortunately, treatment failure due to the emergence of drug-resistant hepatitis B viruses compromises the success of antiviral therapy. Furthermore, the majority of drug-resistant hepatitis B viruses have an altered envelope which may even serve to accelerate the progression to hepatocellular carcinoma. The treating physician needs to ensure that current treatment regimens for chronic hepatitis B prevent active replication, interrupt the progression of liver disease and prevent the emergence of drug resistance.

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Screening for hepatocellular carcinoma

Edward Gane

Abstract

Screening for hepatocellular carcinoma in patients with chronic liver disease has been a controversial issue, despite the devastating outcome associated with delayed diagnosis. The only means to improve outcomes is by earlier diagnosis with regular surveillance of patients at greatest risk for this complication, namely those with cirrhosis and those with chronic

hepatitis B infection. Established screening tests are serum alpha fetoprotein measurement and abdominal ultrasound. The optimal screening interval is six months, based on the average tumour doubling time. Recent studies have confirmed that screening does lead to the detection of hepatocellular carcinoma at an early stage when curative therapy is possible. Survival from the time of diagnosis is improved in screen-detected hepatocellular carcinomas, compared to incidentally detected tumours. In the only randomised control study of surveillance for hepatocellular carcinoma in a population with endemic hepatitis B virus infection, screening was also associated with an overall reduction in mortality from hepatocellular carcinoma. Screening for hepatocellular carcinoma does meet the cost-effectiveness threshold in both the cirrhotic and the chronic hepatitis B virus populations, although the inclusion of transplantation in the latter impacts negatively on cost-effectiveness. Screening for hepatocellular carcinoma is justified in both patients with cirrhosis and those with chronic hepatitis B virus infection.

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Non-surgical treatment of primary liver cancer

Simone I Strasser

Abstract

The majority of patients diagnosed with hepatocellular carcinoma are not able to undergo surgical resection either because of the severity of their underlying liver disease, or because the size and number of tumours precludes such an approach. Liver transplantation is also inappropriate for many patients with hepatocellular carcinoma either because of the extent of disease or limitations in access. A range of effective non-surgical treatments is available for patients of hepatocellular carcinoma, so that now an effective therapy is potentially available to all but those with terminal disease. Commonly used local ablative treatments for patients with smaller tumours include radiofrequency ablation and percutaneous alcohol injection. Transarterial chemoembolisation is most suitable for patients with intermediate stage disease, multifocal tumours without vascular invasion and those with large solitary lesions (>3cm diameter). Recently, targeted systemic therapy with an oral multikinase inhibitor, sorafenib, has shown significant benefit in prolonging survival in patients with advanced hepatocellular carcinoma. Many other targeted drug therapies are in clinical trial development. Combination approaches with radiofrequency ablation and transarterial chemoembolisation, and with radiofrequency ablation or transarterial chemoembolisation with sorafenib or other targeted therapies, are under evaluation. It is critical that patients are staged at presentation with regard to the severity of liver disease, tumour stage and performance status, and that management is undertaken within a multidisciplinary setting to ensure the best outcomes.

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Surgical management of hepatocellular carcinoma

Vincent Lam

Abstract

Hepatocellular carcinoma (HCC) is among the three most common causes of cancer death worldwide. Liver resection and liver transplantation are regarded as the standard curative treatment for hepatocellular carcinoma. Although liver transplantation for early stage hepatocellular carcinoma has been shown to have excellent long-term survival outcomes and low recurrence rates, the shortage of donor liver grafts limits its wide application. Liver resection can be safely performed in patients with early stage hepatocellular carcinoma and preserved liver function. Although postoperative recurrence after liver resection of hepatocellular carcinoma is almost universal, the reported five-year overall survival rates are around 50%. Recently, the concept of primary liver resection and salvage liver transplantation has been proposed in patients with early stage hepatocellular carcinoma and preserved liver function. Universal adoption of either liver resection or liver transplantation for hepatocellular carcinoma is unwarranted and overly simplistic. The use of different therapeutic approaches that incorporate liver resection or liver transplantation, depends not only on the availability of donor liver grafts and waiting time, but also on the expertise of individual centres.

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NSW HBV and liver cancer pilot program: an update on the 'B Positive' Project

Steven Tipper and Andrew Penman

Abstract

The ‘B Positive’ Project, sponsored by Cancer Council NSW, aims to facilitate the earlier detection and optimised management of chronic hepatitis B and hepatocellular cancer. The pilot project in Sydney’s south-west is based on evidence indicating the clustering of hepatocellular cancer cases in NSW, along geographical and ethnic lines. This provides opportunities for devising targeted public health interventions that can bring about significant reductions in the future burden of liver cancer. The project will test the feasibility, acceptability,

and cost-effectiveness of hepatitis B screening and surveillance in individuals with chronic hepatitis B infection and aims to determine what role targeted screening and surveillance may have in preventing the development of liver cancer. This paper outlines the key features of this project, highlighting the development and implementation of the 'B Positive' Project in Sydney's south-west since mid-2007 to early 2009.

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Engaging communities affected by hepatitis B

Jack Wallace

Abstract

The impact of chronic hepatitis B infection on the health care system is increasing. To effectively reduce this burden, the health care system needs to understand how people and the communities most affected respond. Through talking with people with chronic hepatitis B and health workers, the National Hepatitis B Needs Assessment highlights significant gaps in the health care system response to chronic hepatitis B. This article highlights some of these gaps, including poor diagnostic processes, lack of information available about chronic hepatitis B for people who are infected, the need for workforce development (particularly for health and community workers involved with communities most at risk) and issues relating to access to treatment for chronic hepatitis B. The Australian health care system needs to develop effective coordinated responses to chronic hepatitis B before its burden can be reduced.

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