Review Article

Hepatocellular carcinoma in India

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Abstract: Cancers of the liver are one of the commonest cancers that occur in the world, the commonest of which is the hepatocellular carcinoma (HCC). It is considered to be the 5th commonest cancer in the world. In the areas that are endemic for hepatitis B and C, it is extremely common. Unfortunately, India which is an endemic zone for hepatitis B, there has been no comprehensive analyzed data for HCC.

Incidence of HCC in India occurs at two peaks, one at a young age between 40 to 55 years and another above 60 years. Eighty per cent of all HCCs occurring in India occur with cirrhosis of liver in the background and 60% of all these cases are hepatitis B positive carriers. Symptoms are reflective of late presentation with advanced disease.

Surgery, the only curative modulus available, unfortunately is not possible in 95% of HCC patients. Majority of the patients are treated with palliative and supportive care and life spans are limited. Sorafenib is used in a small section of patients. Characterization of HCC with molecular sub-typing is the need of the hour.

Keywords: Liver cancer; hepatoma; epidemiology; characterisation; management; India

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Background

Cancers of the liver are one of the commonest cancers that occur in the world, the commonest of which is the hepatocellular carcinoma (HCC). It is considered to be the 5th commonest cancer in the world. In the areas that are endemic for hepatitis B and C, it is extremely common. Unfortunately, India which is an endemic zone for hepatitis B, there has been no comprehensive analyzed data for HCC. HCC in India occurs in two peaks, one at a young age between 40 to 55 years and another above 60 years. The two peaks occur because of acquiring hepatitis B either in utero or in childhood, or exposure in adulthood (1,2). Eighty per cent of all HCCs occurring in India occur with cirrhosis of liver in the background and 60% of all these cases are hepatitis B positive carriers (3-5). The estimated number of cases per year in India is approximately close to 22,000 with a similar mortality (3).

Etiology

In India, 70% to 80% of all HCCs are related to the hepatitis B virus (HBV), approximately 15% are related to hepatitis C virus (HCV), and 5% to both HBV and HCV (3). Alcohol alone accounts for approximately 8% of all HCCs. In about 10%, no direct etiology is seen. Iron overload and Aflatoxin may have a role to play in some geographical areas in India (3,6).

The prevalence of hepatitis B in India varies between 0.2 to 1.6 per 100,000; 2.77 for males and 1.38 for females. This relative low prevalence is due to an under-reporting of the disease, thus India erroneously falls in the low incidence zone (3,7). The under-reporting of HCC is possibly due to non-surveillance of chronic hepatitis B patients and carriers, and cirrhotic patients (3,7). This also attributes to majority of cases being diagnosed at a late stage of the disease.

The majority of patients with a viral etiology have a silent course, picked up by foeto-maternal transfusion.

Blood transfusion related hepatitis occurs in approximately 3 in 100,000 in India. There is a long gestation period before the cancer develops (8-11).

Clinical features

The common age of presentation (median) is around 52 years; ranging between below 14 years in children and above 60 years in adults, increasing in incidence with age and peaking around 45 to 55 years (2,12). All HCCs occurring in the age group below 14 years are hepatitis B positive (13). Ninety percent of patients are symptomatic at diagnosis. The duration of symptoms is usually from five months to almost a year. About 15% of these patients are diagnosed after one year of symptoms. The clinical presentations commonly seen are anorexia in 60%, fever in odd 25% (14).

Males predominate in this disease in the ratio of 5:1 similar to distributions worldwide (3).

At diagnosis, approximately 10% to 15% are found to have cirrhosis, while on working up it is seen that a further 60% are cirrhotic that is around 70% of the total patient population is cirrhotic. Hepatic decompensation is seen in 50%, with 5% of patients presenting with encephalopathy. Hematemesis and melena occur in 25% (3,13,15) of patients.

Weakness, anorexia, abdominal pain, weight loss, ascites with jaundice, fever and gastro-intestinal bleeding are common symptoms. Patients present commonly with hepatomegaly, pallor, edema, and clubbing (in about 20%). Massive hepatomegaly is seen in about 50% of patients. The enlarged liver is usually firm to hard. Approximately 15% of patients do not have an enlarged liver. About 60% of patients present with ascites while worsening of ascites occurs in about 20%. Sometimes fever, leukocytosis and recurrent hypoglycemia occur as a para-neoplastic syndrome (16,17).

Biochemical and laboratory investigations

The majority of patients are anemic with a mean hemoglobin of 10.8 gm/dL (5.1 to 15.2 gm/dL), and serum bilirubin of 2.5 (0.1 to 30.8). Serum albumin is normal in 1/3rd of patients and mild to be moderately depressed in 50% of patients. Hepatic enzyme disturbances in the form of raised AST, ALT and SAP are seen in 55%, 39% and 33%, respectively (3,13,17).

Serum alpha-fetoprotein (AFP) has a sensitivity of 39% to 65%, specificity of 76% to 94% and a positive predictive value of 9% to 50%. The normal value of AFP in India is around 10 to 20 ng/mL. A level greater than 400 ng/mL (14) which is accepted by European Association for Study of Liver (EASL) as diagnostic, is seen only in 46% of patients, approximately 20% of patients have normal values. Serum AFP values are higher in patients with cirrhotic changes as compared to those without cirrhosis. Fifty-three percent of cirrhotic patients have values greater than 400 ng/mL compared to 26% of non-cirrhotic patients (14,18-23).

Etiological studies

HBV accounts for 73% of all cases of HCC diagnosed using HBV markers as (HBsAg positive-81.3%, HBe antibody positive-7.48%, HB Core positive-9.35%, HBV DNA positive-0.94%). Data on, HBV genotypes is not available. Fifteen per cent are HCV related (of which Anti HCV antibody positive is 95.5%, HCV RNA positive is 4.55%). About 5% patients are co-infected with HBV and HCV. Alcohol accounts for about 8% of cases and, approximately, 9% to 10% have both an alcohol and viral etiology. No etiological cause is seen in 10% of patients (3,6-9,14).

Radiologic studies

Ultrasound is the most common surveillance and diagnostic imaging technique used in India, owing to its low cost, ease of use and low risk. CT scan is also used and may have more definitions than ultrasound.

Forty-eight per cent of all HCCs involve the right lobe, 1/3rd occur in both lobes, while the left lobe is involved in 1/5th of cases. 2/3rd of the tumors are single, large lesions with an average size of 6.8 cm × 6.1 cm. Very large tumors that are greater than 5 cm occur in 75% of patients (3,14).

Small HCCs are seen in only 8%. Three or more lesions are seen in approximately 20% of cases (3,6,14).

Ultrasound appearances are either heterogeneous or hypo-echoic. In CT Scans 23% occur to be hyper-dense.

Vascular invasion of either the major branch or spleno-portal axis or of hepatic veins is seen in more than 50% of patients. The main trunk of the portal vein is involved in about 45%.

Extra-hepatic spread occurs in 15% of which the commonest sites are the peri-portal lymph node or retroperitoneal node in about 60% of these patients and the lung in 15% (3,6,14).

Histopathologic studies

There is a tendency in India to do a fine needle aspiration

(FNA), rather than a core biopsy (3,16). This is often due to fear of bleeding. In fact FNA is done in more than 80% of patients, (the exact number of patients not receiving even this procedure is not known) (3). This leads to an equivocal diagnosis of HCC in approximately 20%. This trend seems to be changing more so in teaching centers and corporate hospitals, with more biopsies being done, helping in the characterization of this disease.

Staging

In India staging is usually done by the TNM and Okuda staging system. This is because of the simplicity of the staging system (3). Based on clinical and radiological data, 73% of patients are seen in Stage III and Stage IV of the disease. In the Okuda Staging, the majority are in Stage II [70] and Stage III [20], hence HCCs are large and very advanced in most cases. The Okuda Staging and TNM Staging are not related to AFP. Advanced Liver Cancer Prognostic System (ALCPS) scoring system, although available is not commonly applied (3,12,13). Majority of the patients have an intermediate ALCPS score (12), in whom it was done. Because of the advanced nature of the disease, the outcomes are poor.

Management

Management and treatment of patients with HCC varies according to various factors which include; patient factors, socioeconomic factors, etiological, as well as the disease status. In urban areas, mainly in tertiary hospitals, all modern facilities for HCC are available, but in rural areas such facilities are scarce and scanty.

Surgical therapy in the form of resection and hepatic transplants are available for early stage disease, in a few centers, and occur possibly in less than 1 in 10,000 patients. Liver transplants done in India are approximately five to six cases in a year. The deterrent factors are cost, availability and patients' ability to withstand (3). Radio frequency ablation (RFA) is available in very few centers but limited experience suggests that RFA may have similar results as hepatic resection in properly selected cases (3,6,17).

Use of trans-arterial chemoembolization (TACE) or RFA is available in some centers, but these are extremely small in number. No organized data is available. Discussion with experts suggests that encouraging results are available for these procedures, even in some advanced cases (1,3).

For advanced liver cancer, there exists no standard chemotherapy for HCC, although sporadic use of doxorubicin, interferon and thalidomide is available, for which there is no organized data. Options of targeted therapy are available. The drug commonly used is Sorafenib. Results suggest that the time to progression is around six months with overall survival of seven months, suggesting an improvement of 40% over Best Supportive Care in these patients. Most patients who were treated on the drug Sorafenib are in Performance Status WHO 0, 1 and 2 and Child Score A and B, and the benefit of this drug seems to be around four months more than the Best Supportive Care. (Unpublished data of 118 patients in India, Bhattacharyya & Datta).

All patients are usually offered Best Supportive Care, which includes management of ascites, nutritional manipulation, treatment of co-morbidities and prevention of deterioration of hepatic functions which includes the anti-virals for hepatitis B and hepatitis C. Most commonly for hepatitis C, pegylated interferon alfa and the anti-viral drug ribavirin, depending on the type of HCV genotype, is used. Most often single drug pegylated interferon is used and viral control is seen in 80%. For hepatitis B lamivudine is usually used as a single drug. Sixty-five per cent of the patients have control of hepatitis B proliferation (9,17).

Prevention of hepatitis B and hepatitis C, which are predominant causes of HCC, is the primary prevention for HCC. Neonatal vaccination of HBV has decreased not only the prevalence of HBV carriers (24) but also the incidence of HBV related HCC.

Increasing awareness of blood bone infection control can also bring down the incidence of hepatitis B and hepatitis C. Therapeutic use of interferon and antiviral in chronic infections of hepatitis can bring down the incidence of viral hepatitis induced HCC (25,26).

Status of clinical trials in India

The number of registered clinical trials in India for HCC is 12 of which epidemiological trials are five and interventional trials for advanced disease is six, of which three are targeted therapy related trials sponsored by multinationals (27).

Conclusions

Treatment and management of HCC remains a challenge. Advanced HCC is not uncommon at diagnosis in developing countries like India, where routine tests for screening are not performed. It is therefore imperative to develop

effective and affordable therapeutic treatment strategies for advanced disease. So far no systemic chemotherapeutic agent other than Sorafenib has shown survival benefit. Multimodality approach is the need of the hour and has shown much better survival benefit, in single modality, in developed countries.

Researchers need to unravel the underlying hepatocarcinogenesis and key molecular targets for development of more effective chemotherapeutic agents to improve survival in advanced HCC.

Vaccination against hepatitis B and antivirals for hepatitis B and hepatitis C in chronic state, screening program for early diagnosis are the challenging task in hepatology for developing countries.

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