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Original Research Article

Clinical profile of hepatocellular carcinoma and experience with sorafenib from a tertiary cancer centre in Southern India

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ABSTRACT

Background: Hepatocellular carcinoma is a major health problem and a major cause of cancer mortality in India. There are no reports published on experience with sorafenib in advanced HCC from India. We analyzed the clinical presentation, possible etiological factors, tumor characteristics, outcomes and tolerability of sorafenib in the patients presenting to present cancer center.
Methods: Retrospective chart review of 53 patients was done. 53 patients (male 37, female 16; median age 52 years, range 7-80 years) fulfilling the diagnostic criteria were analyzed for clinical characteristics, hematological and biochemical investigations, tumor characteristics, treatment taken and outcome.
Results: 53 patients were diagnosed to have HCC between 2012-2015. Hepatitis B virus infection was the most common underlying etiologic factor (22.6%). Heavy alcohol intake was seen in 5 patients. PS ≥2 was noted in 66% of patients. 68% of the patients had BCLC stage C. Sorafenib was well tolerated with median OS of 3 months in patients taking sorafenib.
Conclusions: Most of the patients had advanced inoperable HCC. Majority of the patients presented with BCLC Stage C and D. Hepatitis B infection was the most common underlying etiology. Sorafenib was well tolerated. More prospective studies are required for getting a clearer and correct picture of HCC and experience with sorafenib in Indian scenario.

Keywords: BCLC stage, Clinical profile, Hepatitis B, Hepatocellular carcinoma, Sorafenib, South India

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most malignant tumors with a steadily increasing incidence worldwide.[1] In most countries, hepatocellular carcinoma accounts for majority (70-90%) of the cases of primary liver cancer.[2] Although liver cancer is the fifth most common cancer in the world, overall it has a poor prognosis, making it the second leading cancer in terms of cancer related mortality.[3]

An estimated 14.1 million new cancer cases and 8.2 million cancer deaths occurred worldwide in 2012.[3] According to GLOBOCAN 2012 data, worldwide, HCC is the 5th most common malignancy in males and 9th most common malignancy in females. 82% of the

hepatocellular carcinomas occurred in developing countries, with 55% being in China alone. China, South-Eastern Asia and areas of Africa have a very high incidence (>20/1, 00,000 population) of HCC.[3] HCC is more common in men than in women (male: female ratio of 2.4:1). Most often, hepatocellular carcinoma develops within a background of chronic liver disease. Variations of the causative factors for underlying chronic liver disease explain the epidemiological heterogeneity of HCC.

Information on epidemiology of hepatocellular carcinoma in India is highly fragmented.[4] Cancer registries probably do not accurately reflect the incidence of HCC. Apart from oncologists, HCC is managed by varied specialists like General Surgeons, GI surgeons, Gastroenterologists etc because of which the disease doesn't get registered. Cancer is not a notifiable disease in India. 8 out of 20 PBCRs do not list HCC in the first 10 causes of cancer. Available data indicates that the Age adjusted incidence rate (AAIR) for men ranges from 0.7-7.5 and for women 0.2-2.2 per 1, 00,000 population.[5] Male to female ratio is approximately 4:1. HCC constitutes 4.8% of all cancers. Median age of presentation of Indian patients with liver cancer has been noted to be 40-70 years. Cirrhosis of liver has been noted in 70-90% of patients treated in tertiary cancer centers in India.[6-9] Hepatitis B virus infection has been documented as the probable causative agent in majority of HCC in Indian patients.[6-11] In India, there are approximately 40-50 million HBV carriers and about 10 million HCV carriers. Underreporting of HCC and poor coverage of the entire population partly explains the discrepancy between high prevalence of risk factors and the low reported incidence of HCC.

HCC is a complex disease and has got various etiologies. The major underlying causes for HCC cases are chronic viral hepatitis, alcoholism, cirrhosis, aflatoxin, genetic susceptibility and epigenetic changes. Hepatitis B virus infection is the dominant cause in China, Sub-Saharan Africa and Southeastern Asia regions. Approximately, 195000 cases of HCC (31% of worldwide cases) are attributable to HCV infection. Hepatitis C infection is a more common etiology for HCC in North America and Europe.[12-14] Among patients with HCC in US, 50-60% are infected with HCV, 10-15% are infected with HBV.[14] Approximately 3, 40,000 cases of HCC are attributable to Hepatitis B virus infection. HBV accounts for almost 54% of the HCC cancers worldwide. Many factors increase the risk of HCC in chronic HBV carriers (male sex, old age, family history of HCC, coinfection with HIV or HCV, viral characteristics like genotype, viral load and duration infection, other factors like alcoholism and chronic smoking). The Risk Evaluation of Viral load Elevation and Associated liver disease (REVEAL HBV) study from Taiwan showed that the risk of HCC is proportional to viral load.[15] Increasingly, alcoholism, obesity and Non Alcoholic Fatty Liver Disease (NAFLD) are also being recognized as causative factors of HCC.[16] Aflatoxins are carcinogens produced by Aspergillus species and have been implicated as causative agent in Sub-Saharan African population. Heavy alcohol (>50-70g/day) intake has been shown to cause HCC primarily by causing cirrhosis.

Most of the cases in the west are diagnosed in early stages due to better surveillance rates. However, in India, though there is a high prevalence of HBV infection, the surveillance is poor and majority of the patients are detected in late stages, leading to high rates of mortality.

Data from southern India is lacking. There are no publications regarding sorafenib usage in advanced/ metastatic HCC from India to the best of our knowledge. The present study was designed to study the clinical profile and outcomes of patients on sorafenib of HCC patients in a Tertiary Cancer Centre in Southern India and compare it with published data in other parts of India and the world.

METHODS

This study is a retrospective chart review of Hepatocellular Carcinoma cases registered between 2012to 2015 in our Tertiary cancer care teaching institute in southern India. All cases meeting the EASL diagnostic criteria for HCC were included.[17] Case records with incomplete data were excluded. Patients who were not candidates for surgery and were fit to receive sorafenib were offered sorafenib. Clinical details, biochemical investigations; viral serology, radiological imaging details and details of sorafenib usage were extracted from the records. Patients not on regular follow up were contacted over phone and the status of patients was ascertained. Statistical analysis was done using SPSS software. Outcome of patients on sorafenib was compared with patients who opted for best supportive care.

RESULTS

Clinical profile

53 patients were diagnosed with hepatocellular carcinoma (HCC). There were 37 males and 16 females (male: female ratio 2.3:1) with a mean age of 52.1 years (Table 1).

Table 1: Baseline characteristics of HCC patients in Southern India.

Characteristics	Values
Male	37
Female	16
Sex Ratio (male:female)	2.3:1
Age (mean±SD)	52.1 years (Mean 38 years)
Age Median	46 years
Hindu	47
Muslim	06

The youngest patient was a girl child aged 7 years while the oldest was a 80 year old gentleman. Our tertiary cancer centre receives patients from all over India and also from Bangladesh. 36 patients were from Karnataka, 16 from West Bengal and 1 patient from Bangladesh. 1 patient was diagnosed to have fibrolamellar variant. Clinical profile of the patients is shown in Table 2.

Table 2: Clinical profile of patients.

Symptoms	N = number	Percentage (%)
Symptom duration		
≤ 2 months	26	49
≥ 2 months	27	51
Abdominal pain or discomfort	38	71
Loss of appetite and /or weight	20	37
Abdominal distension	16	30
Lower limb edema	04	7.5
Jaundice	06	11.3
Diarrhea	03	5.6
Vomiting	03	5.6
constipation	01	1.8
Hepatomegaly	40	75
Ascites	11	20.7
Icterus	10	18
Pallor	6	11

Etiologic studies

31 (58%) patients had a tissue diagnosis whereas others were diagnosed based on biomarker, viral serology and radiologic criteria. Hepatitis B virus infection was documented in 14 patients whereas none had HCV infection. Heavy alcohol intake >50g/day, was documented only in 5 patients (Table 3).

Hematologic and biochemical investigations

22 (41%) patients had hyperbilirubinemia. 27 patients had altered AST and ALT levels. 4 patients had albumin less than 3 gm%. Serum AFP levels ranged from 2.5 ng/mL to 30,000ng/mL. 34 (64%) patients had Serum AFP levels >400 ng/mL (Table 4).

Table 3: Etiologic characteristics.

Etiologic agent	Number of patients
HBV	11
HCV	0
Alcoholism	4
HBV+Alcoholism	3
Cirrhosis	8

Table 4: Hematological and Biochemical Investigations.

Parameter	N (%)
Hemoglobin (gm/dL)	Mean 11.2 (±1.74)
Hemoglobin <10gm%	6(11)
Leukocytosis	13(24)
Total Bilirubin >1.2mg	22 (41%)
Raised AST	14 (26%)
Raised ALT	18 (33%)
Alfa fetoprotein (ng/mL)	Mean 1982±6053
Alfa fetoprotein	
<20 ng/mL	6 (11%)
20-400 ng/mL	13 (24%)
>400 ng/mL	34 (64%)

Table 5: Tumor characteristics.

Parameter	Number of patients (%)	AFP range	Median AFP (ng/mL)
Bilobar involvement	35(66%)	2.5-30000	182
2 lesions Right Lobe	2 (0.03%)	70-90	80
Single lesion Right Lobe	8 (15%)	30-3000	358
Single lesion Left Lobe	2 (0.03%)	25-45	35
Largest lesion <2 cm	4 (7.5%)	3-40	20
Largest lesion 2-5 cm	13 (24.5%)	6-3000	353
Largest lesion >5 cm	30 (56%)	2.5-30,000	95 (±1052)

Tumor characteristics

Radiologic imaging (ultrasound and/or Triphasic CT scan of abdomen and pelvis) studies were available in 47 (88%) of patients. 35 patients had multiple lesion both lobes, 10 had isolated lesion and 2 patients had 2 lesions (Table 5). Portal venous thrombosis was noted in 9 patients. Underlying features of liver cirrhosis was seen in 8 patients.68% of patients were in BCLC stage C (Table 6). Sites of metastases are shown in Table 7. Only 2 patients underwent curative surgical resection.

Patients with inoperable and/or metastatic HCC with good performance status were offered palliative

sorafenib. Patients who at least took sorafenib for 30 days and had at least one month of follow up were analyzed. 30 patients were started on full dose (800mg/day) sorafenib, 7 were excluded from analysis.

Table 6: Child pugh (CP) score, ECOG PS and BCLC stage.

Parameter	Number of patients
PS 0	3 (6%)
PS 1	12 (26%)
PS 2	20 (44%)
PS 3 / 4	10 (22%)
CP A	27 (57%)
CP B	20 (42%)
BCLC A	2 (4%)
BCLC B	2 (4%)
BCLC C	32 (68%)
BCLC D	11 (23%)

Table 7: Sites of metastases.

Site of Metastases	Number of patients
Lung only	4
Lung + Adrenal gland	2
Lung + Mediastinal nodes	1
Periportal nodes	3
Ribs only	2
Vertebral metastases	1
Supraclavicular Node metastases	2
Subcutaneous calvarial metastases	1

2 patients underwent dose reduction to 400 mg/day due to skin toxicity and 1 patient had similar dose reduction due to skin toxicity and severe abdominal pain. 34% of the patients stopped sorafenib within 2 months of therapy due to disease progression (21%), symptomatic progression (13%).

1 patient survived for 12 months on sorafenib and died due to progressive disease. Majority of patients tolerated sorafenib well. Fatigue and anorexia were the dominant adverse events (Table 8).

Table 8: Sorafenib toxicity.

Toxicity	All grades	Grade 3-4
Fatigue	11 (47%)	3 (13%)
Anorexia	9 (39%)	1
Hand foot syndrome	5 (21%)	1
Rash	4 (17%)	0
Vomiting	4 (17%)	0
Diarrhea	4(17%)	0
Metabolic abnormalities	4 (17%)	1
Hypertension	3 (13%)	0

DISCUSSION

Clinical profile of HCC has been published from various tertiary cancer centers in India. HCC data from South India is scanty and outcome of HCC patients on sorafenib in Indian patients is not yet reported. Mean age of our patients was 52.1 years which is similar to other reported studies from India. Male to female ratio was 2.3:1. Other studies from India have reported a higher male preponderance.[10,18] Majority (94%) had symptoms at presentation. Abdominal pain or discomfort was the dominant symptom in 38 (71%) patients followed by loss of appetite/weight in 37% of patients. Anorexia (90%) and abdominal pain (80%) were the dominant symptoms in a study from eastern India.[18] Another study from North India too noted weakness and anorexia as the main presenting features.[10] Symptom duration was 1-3 months as seen by most other Indian studies. 75% of our patients had hepatomegaly compared to study by Mukherjee et al where they noted hepatomegaly in all their patients.[18] 60-70%of Indian HCC patients have cirrhosis.[10,18,20] However, underlying cirrhosis was seen in only 15% of the patients in this study. The lower incidence of cirrhosis may be due to the retrospective nature of study and minor features of cirrhosis being missed. The prevalence of HBV positivity in Indian HCC patients ranges between 36-74%.[9,10,20] However, we noted only 26% of our patients with HCC being HBsAg positive. Another major difference is the complete absence of serological evidence of Hepatitis C virus infection. Kumar R et al have reported HBV infection at 73% and evidence of HCV infection in 15% of their patients.[10] As observed in other Indian studies, serum AFP was raised to more than 400 ng/mL in 64% of our patients.[10,18,20]

Sorafenib is an orally administered drug inhibiting multiple tyrosine kinases. Sorafenib is the only agent shown to have some overall survival benefit in advanced HCC. Sorafenib got approval for advanced HCC based on pivotal randomized phase III trials, however the majority of the patients in these trials were in good ECOG PS and most had Child Pugh A status, which is not the case in routine general practice.[21,22] Kostner et al in their retrospective study of sorafenib in HCC, noted median OS of only 1.8 months of patients in PS 2-3.[23] In our study, 66% of our patients had PS≥2. 22 patients on sorafenib had BCLC stage C, with only 1 patient being in BCLC stage B. We observed a median OS of 3 months in patients on sorafenib whereas patients on best supportive care had median OS of 2 months, which is similar to outcomes reported by Kostner et al.[23] Lee et al too report a poor median OS of 4 months and similar toxicity profile of advanced HCC patients on sorafenib.[24]

CONCLUSION

This study results show that HBV infection is the commonest underlying etiological factor for HCC in southern India, consistent with other reports from India. Major differences noted in our study have been absence

of HCV infections and low prevalence of alcoholism and cirrhosis in HCC patients at our centre. Sorafenib was well tolerated in HCC patients with a median OS of 3 months. More data on the treatment efficacy and tolerability of Sorafenib is urgently needed from other tertiary cancer centers in India.

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