ORIGINAL REPORT

Incidence of Hepatocellular Carcinoma in Patients with Thalassemia Who Had Hepatitis C

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Abstract- Hepatitis is the infections of a common cause disease among poly transfused patients. Hepatitis C is slowed progression and inducing HCC. This study assessed HCC incidences, the role of iron and possible antitumor activity of chelators in 170 thalassemia patients using deferoxamine (DFO) therapy. They are diagnosed with Hepatitis C due to positive PCR-RNA. They are Treated with IFN. The follow up program including tests every 3 Months and PCR-RNA, AFP and liver US every 6 months. Whenever there was suspicion of liver malignancy, Biopsy was performed. From the total of 170 patients, 59.4% were male, and 40.6% were female. Mean age of thalassemia diagnosis was 2.69±5.403 (1-41) years and mean Age of hepatitis diagnosis was 17.37±7.263 (3-51) years. 92.4 % of Patient's MT, 0.6 % SS, 2.9% TI. the viral genome was 1a3a. 73.5% of patients had first course of therapy. The frequency of AFP greater than 10 was 5.9%. And the incidence of HCC was 0.6 %(1/170) with a 95% confidence interval. The main risk factor for HCC was HCV infection in TM patients, but it was iron activity in TI patients. Iron chelation with DFO appeared to play a Protective role.

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Introduction

Hepatitis C virus (HCV) infection is a major, worldwide health problem. It is estimated That more than one hundred million people are infected (1,2). Among thalassemia and leukemia patients transfused before the 1990s, these patients acquired HCV infections by transfusion blood or blood product (3,4).

Hepatitis C virus infection is a common cause of liver disease among poly transfused thalassemia. The patients had treated with α interferon 6megunits/m^2 subcutaneously Three times per week plus ribavirin 15mg/kg/day for 24-48 weeks.(5,6) Treatment with Peg interferon alpha produces significantly higher sustain virologic response than treatment with α interferon (IFN) (6).

The aim of IFN therapy for CHC(chronic hepatitis c) is to eradicate the HCV, ending inflammation in the liver, and ultimately obviating the development of hepatocellular carcinoma (HCC) (3).

Chronic hepatitis C with cirrhosis is a major risk factor for HCC. Patients with either HBV or HCV infection have a 3-5% risk of HCC development in a year. Asian studies reported annual incidence of hepatocarinoma in CHC patients of 4-10%, European Studies of 0.5-5%. Several early reports have shown that the risk of HCC increases with the degree of liver fibrosis (7). The mechanism of hepatocarcinogenesis in chronic HCV Infection is still unclear. The ability of the core protein of HCV to modulate gene Transcription, cell proliferation and cell death may be involved in the pathogenesis of HCC (8).

Serum ALT levels serve as adequate necroinflammatory indicators for the liver, low level serum ALT concentration would be suppression of intra-hepatic inflammation, Necrosis, and regeneration and also suppress carcinogenesis, leading to a reduced risk of HCC in IFN treated patients (3,7,9).

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The aim of this study was to evaluate HCC incidence in thalassemia patients. In this study, we investigated the factors associated with HCC in the patients who were following up for more than 5years after INF therapy for CHC in our institution.

Materials and Methods

These present study evaluated 170thalassemia patients with chronic Hepatitis C, who received INF therapy between July 2004 and OCT2010 in Ali Asghar Children's Hospital and who were follow up by periodic check up for at least 5 years after INF therapy.

All patients were positive for the serum anti HCV antibody and for HCV RNA and liver Biopsy were perform on all patients with in prior to INF therapy and patients were Observing for more than 5 years after INF therapy at regular 6 month intervals.

Each follow up included a physical examination, blood tests and measurements of serum alpha fetoprotein and ultrasonography was also performed. If HCC was suspected CT was also performed, and the diagnosis was established histological by liver biopsy. The Results analyzed with SPSS version 17, using $\chi 2$ and t-test.

Results

All TM patients were on iron chelation therapy with deferoxamine (DFO). Demographic and clinical characteristics of the patients was 101 Male patients (%59.4) and 69 female (%40.6) The mean age at diagnosis of underlying diseases were 5.403±2.69 years (range 1-41 years) and the median age of patients at the time of hepatitis were 17.37±7.36 years (range 4-51 years) (Table 1).

Table 1. Age of patient with hepatitis in three course.

	Age diagnosis ofInitialdisease (year)	Age of hepatitis	Duration betweendisease Andhepatitis
Mean	2.69	17.37	14.68
Median	1	17	15
SD	5.403	7.263	6.363
Min	<1 year	3	2
Max	41	51	36

Table 2. Type of diseases with hepatitis.

Type of diseases	No	%	Total
Major thalassemia	164	96.5	96.5
Sickle cell	1	0.6	92.9
Intermedia thalassemia	5	2.9	95.9
Total	170	100	

Underlying diseases Of these 170 patients were in (Table 2).

All patients had chronic HCV infection defined by detectable circulation HCV–RNA. The median viral load in 105 cases was 478569.24 (range 29-5000000 IU/ml) Genotype 1 a, 3a was the most common viral genotype detected at the study (Table 3).

Liver biopsies performed in 121 patients (%68.8) for the evaluation of abnormal serum ALT or for consideration of anti viral therapy or both. The Pathology of chronic hepatitis was based on both grade and stage of liver disease. Iron deposition and portal fibrosis was assessed.

The patients received recombinant IFN 6 mega unit/m² body surface subcutaneous 3 Times a week plus with ribavirin at dose 15 mg/kg/day orally. Of 170 patients 130 (73.9%) received INF plus ribavirin and 66 patients received peg interferon weekly. In this follow up 124 (72.8%) patients had normal ultrasonography (US) after INF Therapy (Table 4). Serum alpha-fetoprotein (AFP) level more than 10ng/ml were seen in 5.9% of patients after INF therapy and who were follow up for at least 5 years.

Hepatocellular carcinoma incidence in this group of patients was 0.6% (1/170) with a 95% confidence interval. The mortality rate was 1.2% (95% confidence interval); one of them due to heart failure and the other had hepatocellular carcinoma whom was not responded to chemotherapy (5).

Table 3. Viral genome in patients with chronic hepatitis C.

Viral genome	No	%
1 a	42	24.7
2 a	1	0.6
3 a	44	25.9
1 a 1 b	13	7.6
3 b	1	0.6
Total	101	59.4
Missing	69	40.6
Total	170	100

Table 4. Results of sonography in5 years follow up in patients with hepatitis C.

Years of follow up	Liver sonography	Abnormal	%
1st year	156	25	16
2nd year	67	23	34.3
3rd year	34	4	11.8
4th year	15	6	40
5th year	170	46	27.1

Discussion

This study found incidence of HCC of 0.6% in this population of TM patients. Chronic hepatitis C infection was the dominant predisposing factor. Infection with hepatitis C virus (HCV) is one of the major long term problems of multi transfused pediatric patients treated for thalassemia 12% to 43% prevalence of exposure to HCV has been reported for these patients (2).

Most patients remain asymptomatic for a long period with liver cirrhosis developing after Approximately 30years (7)Iron hepatic over load and hepatitis C could be progress to cirrhosis and 20% of them to HCC.

Hepatocellular carcinoma following liver cirrhosis as a complication of chronic hepatitis C and iron overload has been reported in thalassemia patients. Association between HCC and iron overload in CHC had been reported (3).

Liver iron overload could lead to immunologic abnormalities that may be associated with Decreased immune care for malignancy. The alteration of immunoregulatory balance can induce suppression of the complement system and of tumoricidal action of macrophages, impairment of lymphocyte proliferation and modulation of cytokine activities, enabling the increased growth of cancer cells (7,10).

Desferrioxamine (DSF) is known to have an antitumor effect on leukemia and neuroblastoma, through its effect on cell cycle control molecules and suggest a protective role of iron chelation therapy against carcinogenesis and its protective effect.

Against the reactivating effect of oxygen radicals, a finally, its depressive effect on proto-oncogene expression (7). Fragatou and *et al*. of Greece has been reported HCC in thalassemia patients. This study assessed HCC incidences, the role of iron and possible antitumor activity of chelators in 57 thalassemia major (TM) and nine thalassemia intermedia (TI) patients using deferoxamine (DFO) therapy (incidence HCC 2/57, 3.5% in TM) and Three (33.3%) in TI patients with liver siderosis and fibrosis and late introduction of iron chelation developed HCC without a history of hepatitis (12). Mancuso was to evaluate HCC incidence in beta-thalassemia. One hundred and eight thalassemia patients have been evaluated, with risk factors (iron overload in 72, HCV infection in 46, HBV infection in two and cirrhosis in 10). Overall, two patients were found to have a newly developed HCC (13).

Azienda in Italian study, had been reported a 2% incidence of new HCC during the follow-up of 105 thalassemia patients (14). Liver enzymes and αFP were elevated in patients with HCC at the time of diagnosis αFP as one of the markers for early diagnosis of HCC (12). In conclusion, further studies of a larger population will be required to define risk factors for HCC in thalassaemic patients. Ultrasonography performed annually, or every 6 months in thalassemia patients would be helpful for early tumor identification.

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