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Effect of Combination Chemotherapy on Hepatitis C Virus in Hepatic Patients

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Abstract: The under lying cause of non-A-non-b hepatitis (NANBH) in most of the cases is Hepatitis C Virus (HCV) which leads to liver cirrhosis and Hepatocellular Carcenoma (HCC). A limitation in the control of the disease is the failure to develop vaccine due to high rate of mutation in viral isolates. Detection of antibodies to HCV is an important indication of past and present infection in enzyme linked immuno sorbent assay (ELISA) but this has many limitations in low risk groups. The most sensitive assay is polymerase chain reaction (PCR) which has detection limit of 2000 viral genomes per ml of human serum. Nine out of fifty patients were selected on the basis of inclusion criteria. Only 4 parameters i.e Total Leucocyte Count (TLC) Erythrocyte Sedimentation Rate (ESR), Serum Bilirubin and Serum Glutamate Pyruvate Transaminase (SGPT) were raised above normal. They returned to normal by chemotherapy indicating the success of treatment but side effects and relapses were also observed. Alpha interferon (αINF) and ribavirin combination chemotherapy has success rate of almost 40%. It is suggested on the basis of study that this combination should not be used as first line treatment, also there is need to educate both doctors and patients to go for liver biopsies for treatment before and after chemotherapy for ensured treatment.

Key words: HCV, chemotherapy, hepatitis patients, PCR, ELISA

Introduction

HCV is the major cause of transfusion associated non-A-non-B hepatitis (NANBH) which leads to viral persistence resulting in Chronic Liver Disease (CLD) followed by hepato-cellular Carcinoma (HCC) and Liver Cirrhosis (Saito *et al*., 1990). HCV patients will be the leading problem of coming years in the medical world (Hoofnagle, 1997).

To date six major genotypes of HCV has been identified. Sub types of each also exist. Typing of HCV viruses is also critical for the investigation of the clinical significance of HCV types in relation to pathogenesis and in particular, response to chemotherapy. Alter *et al*. (1992) reported that 50-80% HCV infected patients develop chronic hepatitis. Out of these infected patients 8-46% develop liver cirrhosis and 11-19% develop HCC (Seeff, 1997). About 10-40% of HCV infection results from transfusion of blood while remaining spread either by sporadic community acquired or by unknown causes (Alter *et al*., 1992) Undoubtedly, HCV is the most common cause of end stage liver failure.

Diagnosis of HCV patients depends on the biochemical findings. Generally ELISA is used for HCV detection but most sensitive is PCR for the determination of infection by amplification of viral sequences which improved the sensitivity of diagnostic procedures. Since antibody testing has many limitations including 2-6 months, window period of seronegativity after acute infection, occassionally false antibody reaction and rarely -ve antibody reaction (Caldwell *et al*., 1993).

Currently alpha interferon (αINF) and ribavirin were used by clinicians for the treatment of HCV infection. Both drugs alone has success rate of almost 20% (Hoofnagle, 1997). However in case of combination chemotherapy achievement is almost 40% (Brillanti *et al*., 1994).

Objectives of the study were to assess the HCV prevalence in hepatic patients and in medical community personnels who have negative antibody test in Faisalabad region, also partial characterization of HCV isolates and to evaluate the efficacy and safety of combination chemotherapy.

Materials and Methods

Out of 50, selected 9 patients were enrolled between Feb. to Oct. 98 having age between 26-60 years and weight between 55-74 Kg when weighed 1st time at clinic. They were confirmed patients of HCV on the basis of ELISA and PCR reports. They had abnormal SGPT values at least for the last 3 months. Patients excluded from study were under 18 years. pregnant or child bearing women, drug addicts, Antibody +ve for HBsAg or HIV+ve.

Patients blood was frozen in ice and serum was obtained at 3000 rpm for 10 minutes and kept at -20°C until analyzed. SGPT levels were determined by liquid UV-Kit method. Serum samples were analyzed for direct and indirect bilirubin. Protein albumin, globulin and prothrombin time from blood. Blood analysis was carried out for the determination of TLC, DLC, ESR and Hb. Urine was analyzed for color, specific gravity and presence of pus cells, RBCs, epithelial cells, crystals, calcium oxalate and uric aid. For PCR, RNA was extracted following the method of Petrelli *et al*. (1994).

cDNA was synthesized by using the protocol of Tisminetzky *et al*. (1994). PCR amplification was performed in DNA thermal cycler by using external sense S' and antisense AS' primers while for N-PCR internal S and A5 primers were used with 1 μL of R-PCR product as template. Agarose gel electrophoresis was performed by following the method of Davis *et al*. (1994) and Sambrook *et al*. (1999).

Results

Blood samples were collected from patients presenting the symptions of weakness, nausea, pyrexia with history of jaundice and yellow appearance. Only nine patients out of fifty presented all three reports of blood urine and SGPT. They were given 3 miu αINF thrice weekly and 1200 mg ribavirin daily in 3 divided doses for 9 months. However to patients of low haemoglobin 600 mg ribavirin was given because ribavirin causes destruction of RBCs.

After 9 months of chemotherapy ESR returned from 130 to 18 mm/hr, similarly TLC came back to normal limits. S. bilirubin returned from 3.1 mg/dl to less than 1.0 mg/dl. However for SGPT fluctuations were observed during the course of chemotherapy especially in patients of low haemoglobin indicating drug intolerance. Over all these prameters returend to normal limits indicating success with combination chemotherapy.

Discussion

Patients were followed for 3 months after discontinuation of treatment with α-INF and ribavirin. The patients continued to have serum SGPT and virologic responses. None of the patients had severe chronic active hepatits (CAH) at 2nd liver biopsy. Greater improvement in piecemeal necrosis and total inflammation and lower incidence of cirrhosis during follow-up suggests that α-INF and ribavirin regimen used can sometimes prevent cirrhosis. Patients with cirrhosis initially had substantial histologic improvement in those with chronic NANBH.

Serum SGPT responses were significantly associated with histologic improvement. α-INF and ribavirin combination therapy suggests that treatment may be discontinued if there is no response after 16 weeks.

We found that patients with histologic improvement at 9 months had about 50% less viremia during follow-up than the patients without improvement at 9 months.

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