INTRODUCTION

Patients with advanced liver disease and cirrhosis secondary to viral diseases have a tendency to develop serious complications of cirrhosis. In Pakistan, hepatitis C (HCV) is a frequent illness and results in decompensation and development of serious complications, which include ascites, esophageal variceal bleeding, hepatic encephalopathy and hepatocellular carcinoma. The course of hepatitis is progressive in these patients and as they reach cirrhotic state, they develop decompensation and their lifespan is limited. Antiviral therapy is commonly not recommended in patients with cirrhosis with signs of decompensation, as they may not tolerate therapy. However, the majority of cirrhotics with HCV infection have reasonably stable hepatic function and after a successful treatment of a decompensating event, they might be suitable candidates for antiviral therapy. Tolerance to antiviral therapy by these patients may be extremely poor due to their advanced disease. However, the only option for them is antiviral treatment, in an attempt to eradicate the virus and to arrest the disease at a stage where they suffer fewer decompensating events and can have prolonged survival. Several studies have been performed in various parts of the world in this subset of patients where standard and Pegylated interferon both have been used. In these studies, sustained virologic response (SVR) has varied from 20 to 58%. The treatment in these patients is especially desirable as cirrhosis has some reversibility. There are other encouraging reports showing that in patients achieving SVR, there is marked reduction in liver related morbidity and mortality. They tolerated therapy reasonably well also. The aim of this study was to analyze the use of standard interferon, ribavirin and amantidine in patients with decompensated cirrhosis in an attempt to eradicate the virus.

METHODOLOGY

The study was carried out at the Department of Gastroenterology at Shifa International Hospital, Islamabad, Pakistan, from January 2007 to January 2012. An informed consent was obtained from all patients prior to initiation of treatment. Patients with chronic liver disease (CLD) secondary to hepatitis C, who had one or more
complications like ascites, hepatic encephalopathy or episode of variceal bleeding were included in the study after an informed consent. Those patients who had variceal bleeding underwent upper GI endoscopy and esophageal band ligation was performed and prophylaxis with propranolol was instituted. Those who had ascites, were managed with dietary restriction and diuretics and when it was optimally controlled, the treatment was instituted. Patients with uncontrolled ascites, recurrent bleeding, or recurrent hepatic encephalopathy were excluded from the analysis. Diagnosis of CLD was based on clinical, laboratory and ultrasonographical features.

Standard interferon alpha-2b 3 miU subcutaneously was administered along with ribavirin 800 – 1200 mg, and amantadine 100 mg b.i.d orally. Other supportive treatment like diuretics, lactulose, propranolol and proton pump inhibitors (PPIs) were continued, as needed. The patients were followed every month with CBC and HCV PCR was performed at 3 months to document early viral response (EVR). Subsequently, they were followed every month with CBC and ALT. HCV PCR was performed at the end of treatment, which was 12 months (ETR). After that, they were followed every month and standard treatment for CLD was continued and HCV PCR was performed at the end of 6 months to document SVR. Those patients who became HCV PCR positive during this period were labeled as relapsers.

The data was collected in a well custom designed proforma and analyzed using Statistical Package for Social Sciences (SPSS) version 16. Frequency and percentage of different variables were determined. Clinical data were presented as mean and standard deviation. Student t-test, chi-square and Fisher exact test applied where applicable. P-value less than 0.05 was considered statistically significant.

RESULTS

Out of 165 patients, 120 were males and 45 were females. The mean age was 45 ± 16 years. The demographic characteristics of patients are shown in Table I.

In 42 (26%) patients, treatment had to be terminated for various reasons. Out of these 42 patients, 16 died (Table II). A total of 123 patients completed the treatment. Twenty-eight (23%) were non-responders. Out of 123 patients, 95 (77%) achieved ETR. Out of these, 58 (47%) achieved SVR, while 37 (30%) patients relapsed (Figure 1).

Outcome analysis showed that patients in child class C were those in whom treatment had to be stopped and some died of complications (Table III).

Those patients who died, predictors of mortality were analyzed. Older age, higher serum bilirubin, higher CPT score and MELD score were found to be factors affecting mortality (Table IV).
Side effects were noted in all patients who were managed with appropriate measures. Haematological side effects were dominant which were managed with growth factors and erythropoietin.

**DISCUSSION**

Hepatitis C is common in Pakistan and treatment with interferon and ribavirin had shown an 80% response in these patients.\textsuperscript{10} Patients with CLD have no hope of getting any improvement unless they are free of the virus. We were able to achieve an SVR of 47% in 123 patients who completed treatment. These results are quite similar to several previously reported studies in such patients. Using standard interferon in low dose and later escalating gradually to 3 miU s/c thrice a week such patients. Using standard interferon in low dose and later escalating gradually to 3 miU s/c thrice a week was due to several complications, which they developed due to fear of profound leukopenia and thrombocytopenia.

Several of these patients (23%) were non-responders. This is likely when disease is far advanced and there are unfavourable factors like genotype-I, obesity, advance fibrosis.\textsuperscript{12} The non-response rate in these patients was higher than has been reported in cirrhotic patients without decompensation.\textsuperscript{10} Other investigators have also reported non-responsiveness in these patients.\textsuperscript{4,6,8} There are not many options left for these patients but only to provide supportive care to prevent further complications.

Relapses were also frequent (39%) in these patients. These rates are considerably higher than patients in chronic hepatitis C without cirrhosis and even those patients who have cirrhosis without decompensation.\textsuperscript{13,14} Some investigators chose to retreat relapsers and non-responders with some success.\textsuperscript{11} These patients could not be convinced to undergo further interferon therapy because of their previous experience with side effects and possibility of decompensation.

In 25% patients, treatment had to be discontinued. This was due to several complications, which they developed (Table II). Although these patients were given supportive treatment with propranolol, lactulose and dietary precautions, several developed hepatic encephalopathy and other complications. Although several of them survived initial decompensating event, some died later with further hepatic complication. Discontinuation rate in several studies has been considerable in this subset of population as 40% had to have treatment stopped in a Turkish study.\textsuperscript{5}

Due to complications, a number of patients died, some on the first complication and some subsequently after another decompensating event. The commonest event was hepatic encephalopathy followed by GI bleeding. When treating this type of high-risk group, such consequences are possible because of advanced nature of disease, as many of these patients develop complications regardless of interferon therapy. Therefore, appropriate precautions are necessary in all CLD patients who are undergoing interferon therapy to prevent these complications, as we did in all of our patients. Along with the progression of liver disease, a reduction in the capability to remove endotoxin and bacteria from the bloodstream, due to an acquired immunodeficiency state in these patients makes them prone to develop complications.\textsuperscript{2}

Standard interferon and ribavirin was used, as used by other researchers.\textsuperscript{7,11} Pegylated interferon was not used due to fear of profound leukopenia and thrombocytopenia in these patients, who already have low platelet counts. Several investigators around the world have used pegylated interferon with ribavirin which was fairly well tolerated.\textsuperscript{4-6,8} However, they reported significant side effects with discontinuation rate of 40%.\textsuperscript{5} Amantadine was used in these patients because previous studies had shown that triple therapy in these hard-to-treat patients gave improved response.\textsuperscript{15,16} Genotypes are not performed in many of these patients because it has been well known that in our country, genotype-II or III are the commonest.\textsuperscript{17} The main goal of treating cirrhotic patients is to achieve an SVR, halt the disease progression, prevent complications and prolong life. American Association for the Study of Liver Disease (AASLD) has recommended individualization of antiviral therapy in them.\textsuperscript{18} However, while treatment of decompensated liver cirrhosis is evolving, the International Liver Transplantation Society guidelines on interferon-based therapy in patients with cirrhosis, recommend strong consideration of treatment in those with a CTP score ≤ 7, and possibly with a score of 8 – 11.\textsuperscript{19} Since there are reports of reversibility of fibrosis,\textsuperscript{20,21} these patients need to be given a chance. While increased use of growth factors in these patients adds to cost of treatment.\textsuperscript{22} With associated complications, this therapy is a tight-rope walk.\textsuperscript{23} The patients of hepatitis C have psychological overlay\textsuperscript{24} and quality of

### Table IV: Factors related to mortality.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>In expired patients (n = 16)</th>
<th>In patients who completed therapy (n = 123)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 13</td>
<td>44 ± 12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CTP score</td>
<td>12 ± 3</td>
<td>8 ± 2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MELD score</td>
<td>18 ± 5</td>
<td>11 ± 3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>11 ± 5</td>
<td>3 ± 2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelets/μl</td>
<td>54000 ± 11000</td>
<td>94000 ± 18000</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

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Journal of the College of Physicians and Surgeons Pakistan 2013, Vol. 23 (12): 833-836 835
life in these patients is impaired. Only long-term follow-up will determine if the SVR improved their quality of life and prolonged survival.

The study has certain limitations. We did not have genotype in these patients and, therefore, could not stratify them in 6 months or 12 months thus, we gave treatment for 12 months to all patients. The viral load on many patients was also not performed due to cost constraints. We used standard interferon with fear that pegylated interferon may cause profound suppression of bone marrow with resultant in leukopenia and thrombocytopenia. The SVR could have been better in these patients if they were treated with pegylated interferon.

CONCLUSION

A 47% sustained viral response was achieved in patients with decompensated chronic liver disease. However, complications did arise during the treatment course, as expected. If these patients have to have a chance to extend their life, antiviral therapy should be offered to carefully selected patients. Thus, they need frequent monitoring and treatment should be carried out at a centre with special expertise.

REFERENCES


17. Khokhar N, Asif N, Khokhar OS. Serotype 3 is most common hepatitis C serotypes in Pakistan: however, significant numbers are untypeable. Hepatology 2003; 38:270-1.


