

PREVENTIVE ROLE OF INTERFERON IN HEPATOCELLULAR CARCINOMA IN NON-RESPONDER HEPATITIS B AND C PATIENTS

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ABSTRACT

Objective: To determine the preventive role of interferon in Hepatocellular carcinoma (HCC) in patients of chronic hepatitis B & C who didn't respond virologically to interferon therapy.

Methodology: This comparative retrospective study was performed in the Medical Unit Hayatabad Medical Complex Peshawar from Jun2014 to April 2015. Patients of cirrhosis liver due to hepatitis C & B virus infection from the wards and hospital OPD were entered. Hbs Ag and Hepatitis C antibodies test was performed on ELISA method. Patients with liver mass on ultrasound and CT scan with raised alpha feto protein were labeled hepatocellular carcinoma were divided in the Child Class A, B or C. They were divided in to two groups, one who used interferon and the other who did not. We noted the reasons for not using interferon and the duration from the earliest evidence of Hepatitis B and C positive status to the diagnosis of HCC.

Results: We collected 500 cases of cirrhosis liver due to hepatitis B & C. Seventy eight percent (n=390) were anti HCV while 22% (n=110) Hbs Ag positive. Fifty three percent (n=265) were male and age range was 45 to 80 years with a mean of 68 +12 years. Their average duration from the diagnosis of hepatitis B & C to cirrhosis liver or HCC was few days to 15 years with a mean of 7.5 + 7 years. Interferon was used in past by 16% (n=80) while 83% (n=415) have not and 1% (n=5) used interferon incompletely. We compared the different parameters between the two groups as shown in (table-1-2) which shows that despite not achieving sustained virological response (SVR) the treated group had significantly lower prevalence of HCC and longer duration from diagnosis to the development of HCC than the untreated cases.

Conclusion: Interferon therapy can delay or prevent HCC in patients of chronic liver disease due to Hepatitis B and C virus even if the patient has not achieved the SVR.

Key Words: Hepatitis C, Hepatitis B, Hepatocellular carcinoma, Interferon, chronic liver disease.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most grievous complication of chronic liver disease due to hepatitis B and C. It accounts for about 90% of all the primary liver cancers¹. It is the third leading cause of cancer related death worldwide². More than 80% of HCC occurs in the Asian and African countries². In 70-90% of cases HCC develops in chronic liver disease³. The incidence of HCC is about 3-5% each year after the development of chronic hepatitis B or C while co-infection increases the incidence. The geographic distribution of HCC follows the distribution of chronic hepatitis B and C⁴.

Chronic hepatitis C is the most common cause of HCC in Pakistan ranging from 60-70% of all the hepatomas⁵. Hepatocellular carcinoma is more common in males as compared to females with a ratio of 3.6:1 and more commonly appears in the 5th to 6th decades of life⁶.

Since the diagnosis of HCC is made mostly at the later stages, treatment modalities contribute little to the overall prognosis⁷. Therefore much of the literature focuses on the prevention of HCC in high risk patients⁸. Screening and early detection is mandatory in the preventive strategies of HCC.

Interferon therapy can delay or prevent HCC in pa-

tients with chronic Hepatitis B and C. The preventive effects of interferon have been studied in different literature with positive results⁹. Interferon therapy can delay or prevent hepatocellular carcinoma even if the patients come in virologically non responding group⁷. Interferon therapy can delay or prevent some other complications of chronic hepatitis B and C even in non responders¹⁰. Most of the related literature compared the prevalence of HCC in patients who responded to interferon therapy verses those who were non responders¹¹. A prospective study reported no significant difference in the prevalence of HCC in those who used interferon versus those who didn't use¹². Though this study reported some benefits of interferon regarding delaying the decompensated cirrhosis liver.

The mechanism of interferon regarding the effects on HCC is debatable. The effect of lowering the viral load may be responsible for delaying or preventing HCC, while other studies mentioned the direct anti tumor effects of interferon on the cirrhotic liver tissue^{13,14}. However interferon has both the mentioned effects¹⁵.

In some parts of the world like ours, it is expected that a significant number of people might not have used interferon therapy in spite of good indications in them. Therefore we compared the prevalence of HCC in non responders versus those who have not received interferon therapy at all.

The motivation to write this paper was to address the important and most frequently asked question by the patient, if they unfortunately come in the non responders, whether they have wasted the money or some benefits are still there? So the aim of this retrospective study was to determine the late benefits of interferon in non responder patients in terms of delaying or preventing HCC due to chronic hepatitis B and C.

METHODOLOGY

This was a retrospective comparative study which was performed in the medical unit Hayatabad Medical complex Peshawar from Jun 2014 to April 2015. About 500 patients of cirrhosis liver due to Hepatitis B & C were randomly collected for the study. Cirrhotic patients, who were Hbs Ag & HCV negative, were excluded from the study. The related data was collected from the patients on a preformed proforma. The important points in the history of the patients noted were, duration from the initial diagnosis of hepatitis B & C, previous use of interferon and the reasons for not using antiviral therapy (interferon) if previously not used. Patients were clinically assessed for child scoring. Serology for hepatitis B & C was performed on ELISA for all the patients. Cirrhosis liver was diagnosed on ultrasound abdomen. The diagnosis of hepatocellular carcinoma was made on presence of mass in the liver on ultrasound and CT scan

of the abdomen with raised alpha fetoprotein level. In a case of normal alpha fetoprotein level, the consistent findings on tri-physic CT were taken as diagnostic for HCC. We divided the patients into two groups, the one who used interferon therapy in the past and the other who did not. We compared the complication profile especially the HCC in the two groups. While calculating the relative risk (RR) and P value, we supposed the treated group as exposed and the untreated group as unexposed to interferon.

RESULTS

We recruited 500 cases of cirrhosis liver from the wards and OPD. All patients were HBs Ag or HCV positive on ELISA. Seventy eight percent (n=390) were anti HCV antibodies while 22% (n=110) were HBs Ag positive. Fifty three percent (n=265) were male and 47% (n=235) were females. Their age range was 45 to 80 years with a mean of 68 + 12 years. Their average duration from the diagnosis of hepatitis B & C to cirrhosis liver or HCC was days to 15 years with a mean of 8.5 + 6 years. We noted that 83% (n=415) of the patients had not used interferon in the past. Amongst these patients, 60.5% (n=247) had not used the interferon because of economic reasons while the rest were not used due to other reasons (Table-3). So we divided the patients in to two groups, the one who had used interferon in the past 16% (n=80) and the other who had not 83% (n=415). One percent (n=5) had used interferon incompletely and were best counted in the untreated group. The differences between the two groups were noted regarding the different parameters especially hepatocellular carcinoma (Table-1). Here HCC (whatever is the child class) is given a separate group from the groups on child class bases. The prevalence of de-compensation (Child Class-C) and HCC was significantly lower in the treated group as compared to the untreated group with decrease in relative risk (RR 0.4536-95%CI-0.2535 to 0.8118 &P=0.0078) and (RR 0.3014-95%CI-0.126 to 0.7212 & P=0.0071) respectively. Similarly these complications occurred in comparatively shorter duration in the untreated group as compared to the treated group. (Table-2)

DISCUSSION

There are many studies we have gone through, which compared the complication profile of hepatitis B & C in the responders with the non responders to interferon. In contrast there is scarcity of the literature on the issue to compare the complication profile of hepatitis B & C in the treated non responders with the untreated patients. Since it is quite common to see the cases of hepatitis B or C who remained untreated in our country as compared to abroad, therefore we realized the need for looking benefits of interferon in term of preventing or delaying HCC in patients who didn't achieved SVR.

Table 1: Comparison of complication profile between the treated & untreated groups

Group	Child-A	Child-B	Child-C	*HCC
Interferon treated	65% (n=52) (total n=80)	21.25% (n=17) (total n=80)	13.75% (n=11) (total n=80)	6% (n=5) (total n=85)
Interferon untreated	28.74% (n=96) (total n=334)	43.4% (n=145) (total n=334)	26%(n=89) (total n=334)	19.5% (n=81) (total n=415)
Relative Risk & P value	0.4536 (95%CI-0.25 to 0.812 P=0.0078			0.3014 (95%CI-0.126 to 0.7212 & P=0.0071

*Patients with HCC were counted separately irrespective of the Child class.

Table 2: Comparison of mean time from the initial diagnosis.

Group	Child-A	Child-B	Child-C	HCC
Interferon treated	1-12yrs (mean=7.5years)	1-14years (mean=8years)	2-15years (mean=8.5years)	4-13 years (mean=10.2years)
Interferon untreated	<15d-5years (mean=2.4years)	2-6years (mean=3.6)	1-7years (mean=3.8)	<15dys-9years (mean=4.3years)

Table 3: Reasons for remaining untreated in our set up.

Reason	Number/% age of patients
Couldn't afford	60.5% (n=247)
Not advised	19.5% (n=81)
Lack of awareness	9% (n=37)
Newly diagnosed	12% (n=50)

This study clearly indicates that interferon therapy and perhaps other antiviral therapy have benefits beyond achieving SVR. The complication profile of treated non responders was better than the untreated patients (table-1). The preventive role of interferon in HCC due to HCV has been mentioned in other literature as well⁷⁻¹⁴.

Omata etal¹⁶ compared the incidence of HCC in three subsets of patients, the one with HCV infection who achieved SVR with interferon therapy versus untreated, the 2nd patients with cirrhosis liver due to HCV who received interferon versus who were untreated and the 3rd patients with HCC who received interferon versus those who were untreated. This study found the preventive or delaying role of interferon on HCC in all the three comparisons.

Similarly some other recent literature showed the prevention of recurrence of HCC with adjuvant therapy of interferon after curative therapy¹⁷. This meta-analysis included 13 randomized clinical trials on the subject. When IFN was used as an adjuvant therapy for HCC patients after curative therapy, the meta-analysis showed that IFN reduced the 1-, 2-, 3-, 4-, and 5-year recurrence rates. Subgroup analysis showed that IFN reduced the 2-, 3-, 4-, and 5-year recurrence rates of hepatitis C viral

(HCV)-related HCC.

Miyake etal reported single-course interferon treatment prevented HCC development (RR 0.45; 95% CI 0.31-0.65). This preventive effect was shown even in nonresponders (RR 0.48; 95% CI 0.25-0.90)¹⁴. This was a prospective study. In our study, we also reported a decrease in the risk of HCC in the treated group as compared to the untreated one. We found the decrease in relative risk for hepatic decompensation and HCC as (RR 0.4536-95%CI-0.2535 to 0.8118 &P=0.0078) and (RR 0.3014-95%CI-0.126 to 0.7212 & P=0.0071) respectively.

Since patients with cirrhosis liver due to hepatitis B & C were collected from the hospital OPD and wards with some health problems/complications, therefore these patients may not be representing all the patients of cirrhosis liver in the society. Similarly as per aim of the study, patients with age 45 or above were collected for the study presuming that HCC is more common in the middle to elderly age group. The greater number of untreated patients in this study reveals indirectly the fact that treated patients have fewer chances to develop complications and so to present to the hospital.

CONCLUSION

This study shows the benefits of interferon therapy in the patients of hepatitis B & C even if no SVR is achieved. The end stage complications of chronic hepatitis B & C especially the HCC, were having significantly lower frequency in the patients who had used interferon in the past as compared to those who has not used.

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CONTRIBUTORS

NS conceived the idea, planned the study, and drafted the manuscript. A helped acquisition of data and did statistical analysis. MS and UK acquisition of data and writing references. All authors contributed significantly to the submitted manuscript.