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ORIGINAL RESEARCH

Role of Pegylated Interferon and Ribavarin in Chronic Hepatitis C in childhood cancer survivors less than 12 years

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ABSTRACT

Purpose: Chronic hepatitis C (CHC) may be seen in cancer survivors due to frequent blood component therapy and parenteral exposures during treatment. Considering the long term adverse effects of CHC, the study was carried to evaluate the response of combination therapy (Pegylated Interferon and Ribavirin) in cancer survivors affected with CHC as direct acting antivirals have still not been approved for children below 12 years age.

Methods: This was a retrospective study carried in cancer survivors below 12 years, who had CHC. They were treated with combination of Pegylated interferon alpha2b 60mcg/m^2/week and ribavirin 15mg/kg/day for 24 or 48 weeks for Genotypes 3 and 1 respectively. Rapid viral response (RVR) and sustained viral response (SVR) were evaluated by PCR at 4 weeks of starting therapy and after 24 weeks of completing therapy. Data on coinfection with Hepatitis B was also evaluated.

Results: Of the 32 patients, 21 were leukemia/lymphoma survivors and 11 were survivors of solid tumours. Genotype 1 was seen in 22/32(69%) and Genotype 3 in 10/32(31%). Hepatitis B co-infection was present in 6 (18.7%) patients. RVR (100% vs 45.5%) and SVR (100% vs 62%) were significantly higher for Genotype 3 as compared to Genotype 1. SVR for HCV was not significantly different in those with HBV coinfection as compared to those without.

Conclusion: Pegylated IFN and ribavirin combination therapy is a successful modality for treating CHC in age group <12 years in childhood cancer survivors where long term morbidities due to Hepatotropic viruses affect the quality of life.

Keywords: Chronic liver disease, Pegylated Interferon, Ribavarin, pediatric,

INTRODUCTION

With the advent of combination chemotherapy, immunotherapy, molecular therapy, stem cell transplant, radiotherapy, advanced surgical techniques and improved supportive care services, the number of pediatric cancer survivors are on the rise. With this, the long term morbidity and mortality with silent killers like Hepatitis B, Hepatitis C and HIV deserves attention. The tiring treatment of cancers with multiple blood transfusions, enormous needle pricks and

numerous hospital admissions predispose them to these dreaded parenterally transmitted infections.

Egyptian study [1] showed high prevalence of hepatitis C virus (HCV) infection among cancer survivors ranging from 33% to 50%. A study from North India [2] showed a prevalence of 60% of HCV in pediatric cancer survivors. Whereas study from Sweden reported the incidence to be very low around 4.8% [3].

Development of cirrhosis in patients with Hepatitis C takes around 25 to 30 years [4]. But rapid progression and exposure to cirrhosis at an early age are emerging concerns in childhood cancer survivors with Hepatitis C [4]. The incidence of cirrhosis in untreated Hepatitis C positive pediatric cancer survivors was high as depicted by few studies, ranging from 9 to 13% [4, 5, 6]. Hepatocellular carcinoma is a hazardous complication and has also been reported among pediatric cancer survivors with hepatitis C [5]. Such high rates of late life-threatening consequences definitely raise an alarm for timely diagnosis and intervention.

Treatment opportunities of Hepatitis C have fluctuated from Interferon (IFN), Ribavarin, Pegylated IFN, combination therapies to Direct acting antivirals (DAA). With the emergence of DAA, the treatment outcomes have reached new horizons. But the restricted spectrum of age and high expenses of DAA have limitations in reaching pediatric cancer survivors in resource constraint settings.

This study was carried for evaluating the response to combination therapy of Pegylated Interferon and Ribavirin in childhood cancer survivors younger than 12 years with Hepatitis C as direct acting antivirals (DAA) are currently not approved in this age group.

METHODS

This retrospective observational study was conducted in the Pediatric Oncology Unit of a public hospital in North India. Study was approved by the institute ethics committee. Case records of cancer survivors aged less than 12 years with Hepatitis C, who had been treated with Pegylated IFN and Ribavirin combination therapy between Jan 2014 to March 2015 were analysed. The treatment regimen followed was as follows: Pegylated interferon alpha2b 60mcg/m^2 subcutaneously once a week and Ribavirin 15mg/kg/day orally once a day. Duration of therapy was 24 weeks for Genotypes 3 and 48 weeks for Genotype 1. HCV RNA viral loads were assessed at 4, 24, 48 weeks of therapy and also after 24 weeks of completion of therapy. Screening for HIV and Hepatitis B virus were done before starting therapy. HBV DNA levels were done for patients positive for HBsAg.

Rapid viral response (RVR) for Hepatitis C was defined as undetectable viral RNA after 4 weeks of starting therapy. Sustained viral response (SVR) for Hepatitis C was defined as undetectable serum HCV RNA 24 week after the end of treatment. Relapse was defined as reappearance of HCV RNA after an end-of-treatment response (i.e. undetectable serum HCV RNA at the conclusion of treatment) had been achieved. Coinfection was defined as detectable HBV DNA by PCR. SVR (Sustained off treatment virological response) for Hepatitis B was defined as virological response (HBV DNA levels <2000 IU/ml) persisting 12 months after cessation of treatment. Persistent transaminitis was defined as ALT/AST > 50 IU/l.

RESULTS

Thirty two children met the inclusion criteria and their records were analysed. Table 1 summarises the baseline characters of these children. Hyperbilirubinemia (Total serum bilirubin >2mg/dl) was seen in only one patient while transaminitis was seen in 17/32 (53%) patients. None of the patients were infected by Genotype 2. None of the patients had HIV.

Conventional adverse effects of IFN combined therapy like flu like symptoms, headache, insomnia, fatigue was seen in almost all the patients. Nausea and vomiting was seen in one

third of the patients. Weight loss (10% in 6 months) was found in 15% of the patients. No neuropsychiatric complication was noted. Overall IFN combination therapy was tolerated well. There was no dose delay of more than 7 days in 30 patients. However in 2 patients we had to hold IFN therapy at 10 weeks and 16 weeks as they developed side effects like severe pallor with bleeding due to superseding Parvo virus B19 infection.

RVR was seen in 20/32 (62.5%) of the patients in which Genotype 3 had significantly better response when compared to Genotype 1 (Table 2). SVR was found in total of 23/31(74%) patients and was significantly high for Genotype 3 (Table 2). There was no difference between those who attained SVR vs those who did not in terms of coinfection with Hepatitis B, median viral load and gender. With a median follow up duration of 54 months, there was no relapse reported.

Coinfection with Hepatitis B was present in 6/32 (18.7%). All these 6 children received Entecavir in addition to the combination therapy of IFN and Ribavirin. Of these 6, 2 children (33%) attained SVR for Hepatitis B at the end of IFN therapy. 4 out of these 6 patients had transaminitis and one of these four attained SVR for Hepatitis B by the end of therapy.

DISCUSSION

In the present study we describe the response to combination therapy with Peg IFN and ribavirin in childhood cancer survivors with Hepatitis C. We had a higher percentage of patients of leukemia/lymphoma when compared to solid tumors which is comparable with most of the studies [7] due to increased exposure of blood and blood products in this group as compared to solid tumors.

Two genotypes (Genotype 1 & 3) were isolated and Genotype 1 was found in higher number (69%) of the patients. Messina et al [8] states that in a general non cancer population Genotype 3 was found in 71% of the patients from South Asia. In studies involving cancer survivors (3, 5, 6, 8, 9) Genotype 1 predominates and that has been reported as a predominant genotype among patients undergoing multiple blood transfusions [8]. Concentration of the patients with a similar genotype in our setup also points towards similar mode of transmission as our cohort utilized similar hospital services in terms of blood and blood product transfusions.

We had a higher RVR and SVR as compared to other studies [6, 7, 9] and this was despite the fact that most of our patients had genotype 1. Also the RVR and SVR was significantly high among patients of Genotype 3 versus Genotype 1. Study by Caesaro et al [9] reported SVR of 40% with combination therapy and best response was noted in Genotype 2 Vs Genotype 1 and this was further supplemented by a systematic review [10] which demonstrated a higher response with genotype 2 and 3 than 1 and 4.

HCV genotype 3 has been strongly associated with steatosis, fibrosis and increased oncogenesis [11]. It has been considered a villain [11] when it comes to treating it with DAA in adults which on the other hand has excellent responses in children treated with peg IFN and Ribavarin. In our study all the patients of Genotype 3 attained SVR which was significantly higher than Genotype 1. In fact in 2 of our patients we had to hold the therapy at 10 weeks and 16 weeks due to side effects and still they attained SVR. It is worth mentioning here that both of them had low viral loads which has also been analysed by a meta-analyses [12] which says that a reduction in treatment duration does not lower the chances of curing Genotype 2 & 3 as long as the duration of therapy is at least 16 weeks and the ribavirin dose is weight-adjusted.

Direct-acting antiviral (DAA) medications have been recommended as the treatment of choice for Hepatitis C in patients more than 12 years of age. Treatment protocols in age less than 12 years has to be individualised. In fact a position paper by ESPGHAN [13] suggests that in most cases, treatment of children younger than 12 years could be postponed until the

expected extension to the existing age indication for DAAs is granted. However this statement was given for general non cancer population but keeping in mind the childhood cancer survivors' profile and increased incidence of long term complications in them, there might be a need to redesign this statement for our patient cohort and early intervention with existing approved drugs may be followed. There had been few trials of DAA in children less than 12 years which show promising results but till the time no formal guidelines are drawn for this group, we may continue to give peg IFN and ribavirin. This statement is quite relevant for Genotype 3 where treatment given even for smaller durations can achieve SVR.

Viral load >2*10^6 was not found significant in achieving SVR in our patients which was contrary to other studies [14, 15]. In fact viral load was lower in our subgroup of patients when compared to other studies [14]. However in our study we had 4 patients (all of Genotype 1) in which the RVR was negative but in due time attained SVR and 3 of these 4 patients had viral load >2*10^6.

Gender did not seem to effect SVR in our study which was demonstrated by [15] where females had better outcomes because the poor outcomes of males have been reported due to the higher viral load among males. This points out the poor health seeking behaviour for females in our patient cohort as only 6 females consented for the study.

Accelerated cirrhosis, increased severity of liver disease along with increased risk of carcinogenesis have been reported with coinfection compared to both HBV monoinfection and HCV monoinfection [16]. Coinfection with HBV was found in 18.7% of the patients which was comparable to an Indian study [2] however studies from Turkey, Egypt and US report low prevalence of 2-4% [1, 4, 17]. At present there are no specific recommendations for children <12 years with coinfection [16]. Also in this age group the treatment options are quite limited for both the viruses individually. Pegylated Interferon seems to be a promising option in both HBV and HCV hepatitis. It is worth mentioning here that there was no HBV reactivation in either of the two children who had cleared HBV. Reactivation has been reported to be around 50% with IFN based therapy in some studies [16].

The limitation of our study was a smaller cohort of patients. We were unable to do liver biopsy and histological correlation. In coinfected children we didn't have data of HBe antigen positivity. Our follow up period was only for 54 months. Strengths of the study include supervised treatment of peg IFN and ribavirin, and stringent testing and follow up for RVR and SVR in all children. Also, we didn't have any abandonment and patients compliance was good.

We conclude that Pegylated IFN and ribavirin combination therapy is a successful modality for treating patients with chronic Hepatitis C in age group <12 years in childhood cancer survivors where long term morbidities due to Hepatotropic viruses can affect the quality of life to a significant extent. In a resource constraint setting like ours where DAA are still not freely available and also specially where the age group itself becomes a limiting factor for administering DAA, there is a possible role of pegylated IFN and Ribavarin.

ABBREVIATIONS

CHC	Chronic Hepatitis C
RVR	Rapid Viral Response
SVR	Sustained Viral Response
PCR	Polymerase Chain Reaction
HCV	Hepatitis C
ALT	Alanine transferase
IFN	Interferon
DAA	Directly Acting Antivirals

Table 1: Baseline characteristics of patients

Median age (range)	**10 years (2.5 to 12 years)**
Sex Male Female	 26 (81.25%) 6 (18.75%)
Primary cancer Leukemia/lymphoma Solid tumours	 21(65.6 %) 11(34.4%)
Genotypes Genotype 1 Genotype 3	 22(68.7%) 10(31.3%)
Median viral load at baseline in IU/ml(range)	1.36*10^6 (1.2*10^3 to 1.8*10^7)
Median SGPT in IU/L (range)	52.5 (24 to 244)
Median Total Bilirubin in mg/dl (range)	0.5 (0.1 to 2.1)
Hepatitis B Co-infection	6 (18.7%)
Rapid Viral Response (RVR)	20 (62.5%)
Sustained Viral Response (SVR)	23 (74%)

Table 2: Comparison of response to treatment between Genotype 1 and 3

S No.	**Variables**	**Genotype 1 (%)**	**Genotype 3 (%)**	**p value**
1	Number of patients (N=32)	22 (69)	10 (31)	-
2	Median viral load (Range)	1.2*10^6 (1.2*10^3-1.8*10^7)	1.4*10^6 (3.4*10^4-1.5*10^7)	1
3	RVR	10/22 (45.5)	10/10 (100)	0.004
4	SVR	13/21* (62)	10/10 (100)	0.03

*One patient had relapse of the primary cancer and died during IFN therapy so SVR could not be evaluated in him

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