Efficacy of Ribavirin to Prevent Hepatitis Reactivation in Hepatitis C Virus-infected Patients Treated for Non-Hodgkin Lymphoma

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Background and study aims: Reports have found an association between B cell non-Hodgkin lymphomas (NHL) and Hepatitis C virus (HCV) infection. However, data on acute exacerbation and reactivation of chronic HCV infection following chemotherapy are very limited. We studied the efficacy of ribavirin to prevent hepatitis reactivation in HCV-infected patients treated for NHL.

Patients and methods: This study was carried out at Medical Oncology & Hematology Department , Zagazig University Hospitals. It included 57 patients with B-cell NHL who were naïve to chemotherapy, among them 24 patients were positive for HCV and 33 patients were negative for HCV (group C). The HCV positive group were subdivided into 11 patients who received ribavirin (group A) and 13 patients did not receive ribavirin (group B). Routine investigations for NHL were done, HCV RNA was measured for HCV positive patients before and after the end of chemotherapy.

Results: HCV infection occurred in 42% of patients with B cell NHL. Acute hepatic enzyme exacerbation occurred in 8 (14%) of all patients with the highest percentage was 29.2 % among HCV infected patients (7/24), while only one patient (3%) in the HCV negative group (p= 0.007). Among the 24 NHL patients with HCV positivity, we compared group A versus group B during chemotherapy as regards to hepatic enzyme flare, it was (27% & 30%, respectively, p= o.6). Five (20.8%) of 24 NHL patients with HCV positivity developed HCV PCR reactivation; 2 patients of group A and 3 patients of group B (18.2% & 23.1%, respectively, p= 0.58). The outcome was comparable between the three groups.

Conclusion: The frequency of HCV infection in patients with B cell NHL is higher than in the general population. Acute exacerbation and reactivation of chronic HCV infection occur in a sizeable subset of patients with NHL during chemotherapy. The use of ribavirin did not decrease hepatic enzyme flare or HCV PCR reactivation during chemotherapy.

INTRODUCTION

Hepatitis C virus (HCV) infection is endemic in Egypt. Many reports have found an association between B cell non-Hodgkin lymphomas (NHL) and HCV infection. The role of HCV infection in lymphomagenesis may be related to chronic antigenic stimulation of HCV [1]. However, little is known about acute exacerbation and reactivation of chronic HCV infection in patients with cancer [2]. Most of the reported cases of liver dysfunction in HCV-infected cancer patients occur in non-Hodgkin lymphomas [3]. Authors have reported a reactivation of HCV replication in patients with CD20-positive B-cell NHL under Rituximab-based chemotherapy [4].

Also, limited studies indicate that episodes of acute exacerbation of chronic HCV seem to be less severe than similar episodes of chronic hepatitis B virus (HBV) exacerbation [5]. As reactivation of the HBV after cytotoxic chemotherapy is common in clinical practice. Thus, prophylactic antiviral (lamivudine) treatment should be started at the initiation of chemotherapy and maintained for at

least 6 monthes following the completion of therapy [6].

In our study, in analogy with the use of lamivudine as prophylaxis against HBV reactivation, we tried to use Ribavirin (a synthetic nucleoside analogue) as a prophylactic antiviral treatment to reduce the risk of HCV reactivation and severe hepatitis flares.

We sought to determine the frequency of HCV infection among B cell NHL patients, also to determine the efficacy of ribavirin to prevent hepatitis reactivation in HCV-infected patients treated for NHL.

PATIENTS AND METHODS

The study is a randomized controlled intervention trial, that was carried out at Medical Oncology and Hematology Department , Zagazig University Hospitals between July 2010 and August 2012. It included 57 patients with NHL who were naïve to chemotherapy, among them 24 patients were positive for HCV infection & 33 patients were negative for HCV infection (group C). The HCV positive group was subdivided into 11 patients who received ribavirin (group A) and 13 patients without ribavirin (group B) (figure1).

Inclusion criteria:

1. Age: > 18 years.
2. Sex: Both sexes were eligible.
3. Pathological proof of B-cell non- Hodgkin's lymphoma.
4. Adequate bone marrow reserve.
5. Adequate liver and kidney functions.
6. Eastern Cooperative Oncology Group performance status (PS) of ≤ 2.
7. All patients were naïve for anti-HCV treatment.
8. All patients were chemotherapy naïve.

Exclusion criteria:

1. Prior or concurrent second malignancy.
2. Pregnant, lactating females.
3. Medical contraindication for receiving the study treatment as patients with active or uncontrolled infection.
4. Positivity for HBsAg or HBcAb or HIV.
5. Non-viral causes of liver affection.

Methods:

Informed consent was obtained from participants. (females must accept to use contraception during treatment). All participants were subjected to:

1. Thorough history taking, clinical examination.
2. Complete blood counts.
3. Serum Lactate dehydrogenase (LDH).
4. Erythrocyte sedimentation rate (ESR).
5. Liver and Kidney function tests (ALT ,AST ,Serum billirubin, serum albumin, INR and serum Creatinine) .
6. Viral markers (HBs Ag, HBcAb , HCV Abs) and HCV RNA in serum by PCR if HCV antibodies were positive.
7. Autoimmune Hepatitis antibodies (antinuclear antibody (ANA), anti-smooth muscle antibody (SMA), liver/kidney microsomal antibody (LKM), anti soluble liver antigen (SLA/LP) and anti-mitochondrial antibody (AMA)).
8. Serum electrolytes (Na, K & Ca), Serum uric acid and fasting blood sugar.
9. Bone marrow Biopsy.
10. Echocardiography and radiological studies were performed including: chest radiograph, CT scans of abdomen and pelvis and CT scans of the neck and thorax if any abnormality is noted or suspected on the routine chest radiograph (for staging).

HCV RNA examination

HCV RNA in serum was done at the beginning and at the end of chemotherapy. It was quantified using a commercially available polymerase chain reaction method (COBAS TaqMan HCV Test; Roche Molecular Systems, Branchburg, NJ) with a quantification range from 43 to 69,000,000 IU/ml [7].

Treatment plan:

Chemotherapy were given based on the pathological sub-types either indolent or aggressive NHL. Detailed history, full clinical examination and Laboratory assessment were performed before each treatment cycle. All patients who ended the first 4 cycles of treatment were eligible for reevaluation within 2 to 3

weeks, and those who responded (complete response [CR] or partial response [PR]) were completed the therapy to a total 6 cycles.

We randomly divided the patients with positive HCV infection into two groups, one group received Ribavirin 1000- 1200 mg daily orally during the course of chemotherapy and the other did not.

Definitions:

Acute exacerbation of chronic HCV infection was defined as a 3-fold or greater increase in serum ALT level in the absence of the use of hepatotoxic drugs (other than chemotherapeutics), or other systemic infections (including hepatitis A, HBV and human immunodeficiency virus infections) [5]**.**

HCV reactivation was defined as an increase in HCV viral load of at least 1 log10 IU/ml over baseline following chemotherapy or immunosuppressive therapy, as chronically infected patients have stable HCV RNA levels that may vary by _0.5 log10 IU/ml [8]**.**

Response criteria:

According to Revised response evaluation criteria in solid tumors (version 1.1) [9].

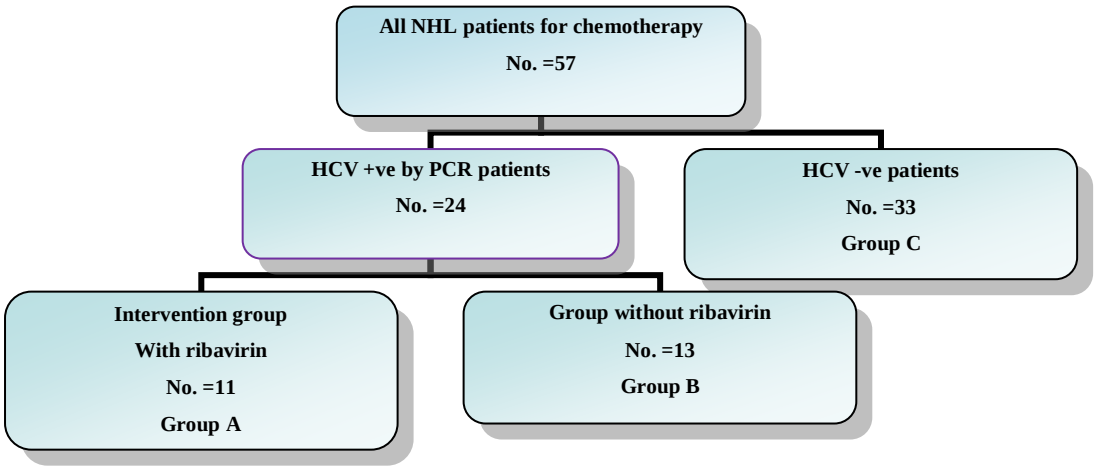
Statistical Analysis

All the data were managed using SPSS-version version 20.0. A two-sided P value of less than 0.05 was considered to indicate statistical significance. The association between categorical data was tested by Chi-square and Fisher exact tests. The t-test was used to assess whether the means of two groups were statistically different from each other. To compare between more than two groups, one way analysis of variance (ANOVA) was used. Survival analysis was done according to Kaplan-Meier method, and compared by log-rank test.

Overall survival (OS) was calculated as interval (by months) between date of randomization (pathology date) till date of death or date of last follow up.

Disease free survival (DES) was calculated as the period of time patient lived without evidence of disease relapse (for responding patients) .It is the interval (by months) between date of the complete response till date of disease progression or date of last follow up[1].

Figure (1) shows the distribution of the study groups



RESULTS

The base line characters of all patients are described in (table1). In our study, HCV infection occurred in 42% of patients with B cell NHL. Acute hepatic enzyme exacerbation occurred in 8 (14%) of all patients, and with the highest percentage (29.2 %) among HCV infected patients (7/24), while only one patient(3%) in the HCV –ve group (p= 0.007). Among the 24 NHL patients with HCV positivity , we compare patients who received ribavirin (group A) versus those who did not receive ribavirin (group B) during chemotherapy as regards to hepatic enzyme flare which was (27% & 30%, respectively, p= o.6). Five (20.8%) of 24 NHL patients with HCV positivity developed HCV PCR reactivation; 2 patients of group A and 3 of group B patients (table 2 and 3). There was a significant relation between HCV reactivation and hepatic enzyme flare (p <0.001) (table 5).

Only 3 patients (37.5%) form those who developed hepatic enzyme flare stopped their chemotherapy ,while none from the other group stopped chemotherapy , there is a statistical significant difference (p = 0.002) (table 4).

In this study the overall survival and disease-free survival in the three patients groups were comparable, although many patients among the HCV infected NHL group showed some delay in the treatment schedule, but this follow up was short (figure 2).

In the terms of overall response , 63% of our patients achieved complete response (CR) and 28% partial response (PR); 76% of DLBCL (30/39) patients obtained a CR, while between indolent NHL patients 21% (3/14 patients) achieved CR. While, among HCV positive NHL, 73.3% (11/15 patients) of DLBCL achieved CR, whereas, 33.3% (3/9 patients) of an indolent NHL achieved CR (p-value = 0.07).

Table (1): Patient characteristics of the studied groups.

Variable		HCV positive patients		HCV negative patients	p-value
		Received Ribavirin Group A (11) No (%)	Without Ribavirin Group B (13) No (%)	Group C (33) No (%)	
Age (years)	Mean + SD	45 + 15.9	52 + 6.5	49 + 13.7	0.496
Sex	Male	6 (54.5%)	5 (38.5%)	19(57.7%)	
	Female	5 (45.5%)	8 (61.5%)	14(42.4%)	0.50
PS	PS=0,1	10(90.9%)	11(84.6%)	29 (87.9%)	
	PS=2	1 (9.1%)	2 (15.4%)	4(12.1%)	0.895
Clinical	LN(only)	7 (63.6%)	6 (46.2%)	20 (60.6%)	
	Splenomegaly	3 (27.3%)	5 (38.5%)	5 (15.2%)	0.424
	Extranodal	1 (9.1%)	2 (15.4%)	8 (24.2%)	
Stage	I	0 (0 %)	1(7.7%)	4 (12.1%)	
	II	2 (18.2%)	3 (23.1%)	15 (45.5%)	0.224
	III	4 (36.4%)	6 (46.2%)	9 (27.3%)	
	IV	5 (45.5%)	3 (23.1%)	5 (15.2%)	
LDH	Normal	0(0 %)	0(0 %)	2(6.1 %)	0.471
	High(> 234)	11(100%)	13(100%)	31(90.9%)	
IPI	Low risk	1 (9.1%)	3 (23.1%)	11 (33.3%)	
	Low-intermediate risk	8 (72.7%)	8 (61.5%)	18 (54.5%)	
	High intermediate risk	2 (18.2%)	2 (15.4%)	3 (9.1%)	0.572
	High risk	0(0 %)	0(0 %)	1 (3.0%)	
Pathology	DLBCL	8 (72.7%)	7 (53.8%)	24 (72.7%)	
	Indolent NHL - marginal zone lymphoma - small lymphocytic lymphoma - Mantle cell lymphoma - Lymphoplasmacytic lymphoma	3 (27.3%) 1 (9%) 0 (0%) 1 (9%) 1 (9%)	6 (46.2%) 2 (15.3%) 3 (23%) 1 (7.6%) 0 (0%)	5 (15.2%) 0 (0%) 4 (12.1%) 1 (3%) 0 (0%)	0.130
	Burkitt	0(0%)	0(0%)	4 (12.1%)	
Chemotherapy	CHOP	8 (72.7%)	7 (53.8%)	24 (72.7%)	
	-COP	3 (27.3%)	5 (38.5%)	5 (15.2%))	0.165
	-HyperCVAD	0(0 %)	0(0 %)	4 (12.1%)	
	-FC	0(0 %)	1 (7.7%)	0(0 %)	

LN = Lymphadenopathy, DLBCL =diffuse large B-cell lymphoma, IPI = International Prognostic Index

Table (2): Frequency of hepatic enzyme flare among the three studied groups .

Enzyme flare	HCV positive patients				HCV negative patients		P value
	Received Ribavirin Group A (11)		Without Ribavirin Group B (13)		Group C (33)		
	No	(%)	No	(%)	No	(%)	
No enzyme flare	8	72.7	9	69.2	32	97	0.019*
With enzyme flare	3	27.3	4	30.8	1	3	

Table (3): Comparison between HCV positive patients who received ribavirin (group A) versus those who did not receive ribavirin (group B) regarding hepatic enzyme flare & HCV PCR reactivation

Variable	HCV positive patients				P value
	Received Ribavirin (11)		Without Ribavirin(13)		
	No	(%)	No	(%)	
Enzyme flare:					
-No	8	72.7	9	69.2	0.605
-Yes	3	27.3	4	30.8	
PCR reactivation:					
No	9	81.8	10	76.9	0.585
Yes	2	18.2	3	23.1	

Table (4): Frequency treatment disruption among the studied groups of patients according to hepatic enzyme flare

Variable	Hepatic enzyme flare				P value
	No enzyme flare(49)		With enzyme flare(8)		
	No	(%)	No	(%)	
Chemotherapy course:					
-completed	49	100	5	62.5	0.002*
-stopped	0	0	3	37.5	

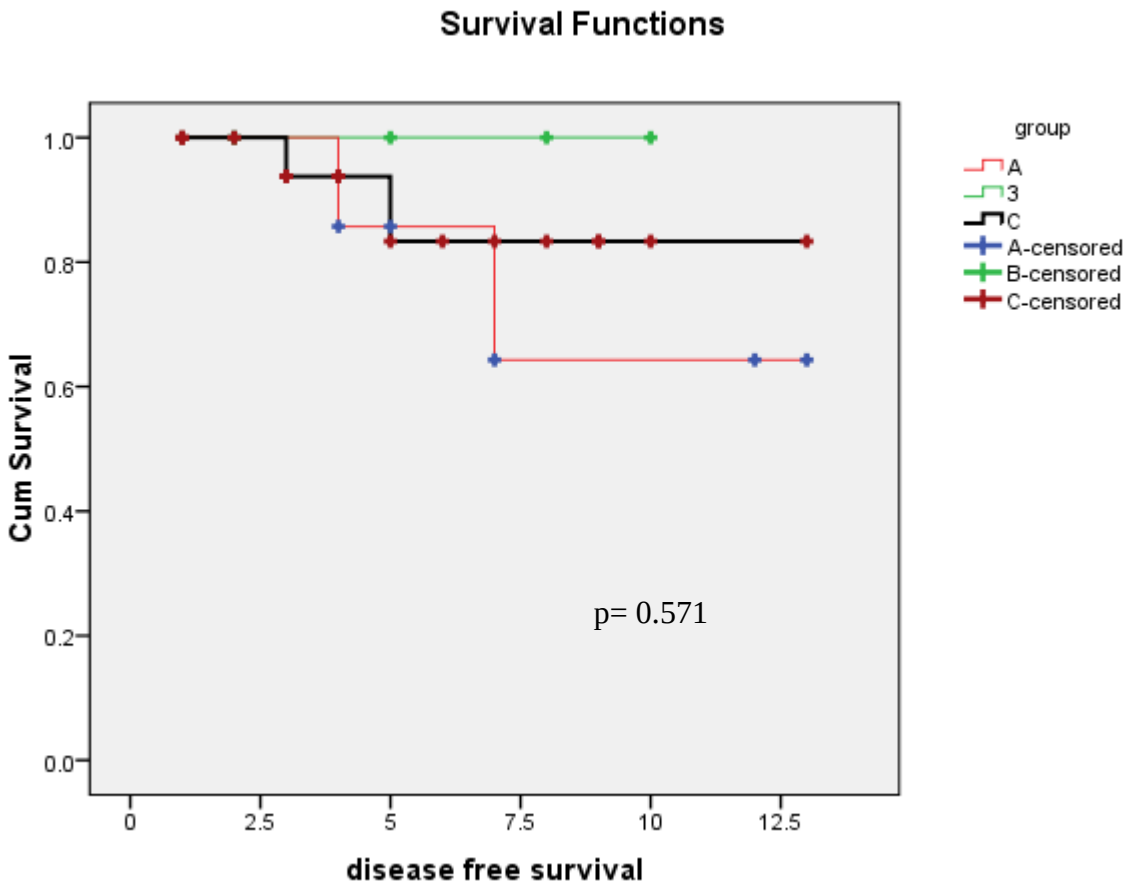
Table (5): Relation between HCV PCR reactivation in NHL patients with HCV positive and hepatic enzyme flare:

VARIABLE	HCV POSITIVE NHL PATIENTS				P VALUE
	No HCV PCR reactivation (N=19)		With HCV PCR reactivation (N=5)		
	No	%	No	%	
Enzyme flare:					
-No	17	89.5	0	0	< 0.001*
-Yes	2	10.5	5	100	

Table (6): Distribution of treatment response among the studied groups of patients according to HCV status

Response	HCV positive patients				HCV negative patients		P value
	Received Ribavirin Group A (11)		Without Ribavirin Group B (13)		Group C (33)		
	No	(%)	No	(%)	No	(%)	
Responders -Complete	8	72.7	6	46.2	22	66.7	0.329
Non-responders	3	27.3	7	53.8	11	33.3	
-Partial	3	27.3	5	38.5	8	24.2	
-Stable	0	0.0	1	7.7	3	9.1	
-Progression	0	0.0	1	7.7	0	0.0	
Total	11	100	13	100	33	100	

Figure (2): One year disease-free survival



DISCUSSION

The percentage of HCV infection among B cell NHL patients is 42 % (24 out of 57 cases) which is in agreement with and equal to results obtained by Cowgill et al.[10] (a study conducted at Cairo University hospitals, Egypt on 220 patients and the prevalence of HCV infection was 42.7 %), while Coppola et al. [11] (a study conducted in Italy on 36 patients and the prevalence of HCV infection was 22 %).

The interesting finding in our study is that percentage (42 %) of HCV infection which is higher than that observed in the general population (15-20%) [12]. This comes in agreement with Nosotti et al. [3], who stated that the prevalence of HCV infection among NHL patients was 9.2%, this prevalence is also higher than that observed in the general population in Italy (3%). This association between B cell non-Hodgkin lymphomas (NHL) and HCV infection may be related to chronic antigenic stimulation of HCV.

In this study, the comparison between HCV positive patients versus HCV negative patients with NHL showed no statistically significant difference as regard age, sex, clinical presentation, stage , IPI score, PS status ,LDH level, pathological type , chemotherapy regimen, ,this comes in concordance with results of Marignani et al.[13]**.** Most of our HCV positive patients (75%) presented with advanced stage (III/IV) compared to 42.5% among HCV negative patients (p-value =0.09), this result was similar to the study of Luppi et al.[14] who reported that the percentage of advanced stage (III/IV) was 74% of HCV positive patients ,while 64% of HCV negative patients.

In the present study, 14 patients (24.5%) had an indolent NHL and 43 patients (75.4%) had an aggressive NHL. The most frequent pathological type was DLBCL. The highest percentage (37.5%) of Indolent NHL type was found among HCV positive NHL cases (9/24 patients), especially marginal zone lymphoma (3 patients). This result is in concordance with Arcaini et al**.** [1] who reported that 37% of HCV positive NHL cases (59/160 patients) had an indolent NHL type, while 62% of the cases had a DLBCL type.

In the terms of overall response , 63% of our patients achieved complete response (CR) and 28% partial response (PR); 76% of DLBCL (30/39) patients obtained a CR, while between indolent NHL patients 21% (3/14 patients) achieved CR. While, among HCV positive NHL, 73.3% (11/15 patients) of DLBCL achieved CR, whereas, 33.3% (3/9 patients) of an indolent NHL achieved CR (p-value = 0.07) . While, Pellicelli et al. [15] showed that 54% of DLBCL achieved CR and 55% of indolent NHL patients achieved CR. In our study, no statistically significant difference was found when we compared the CR rates in the three groups.

Among the 57 NHL patients in our study, patients (14%) developed hepatic enzyme flare. The highest percentage of enzymatic flare was among HCV infected patients (29.2 %) , while only one patient (3%) in the HCV negative group (C). There was a statistical significant difference (p= 0.007) between the two groups. This result comes in agreement with another study which reported that among the HCV-infected subjects, the incidence of hepatitis flares was 26.3% vs 2.1% among the HCV-uninfected individuals [3].

We found that 20.8% of HCV infected NHL patients (5/24 patients) developed HCV PCR reactivation. Also, Parag et al [5] reported that 36.3% of HCV infected NHL patients proved by PCR (8/22 patients) developed HCV PCR reactivation. While, Boyle et al. [16] reported that 66.6% of HCV infected NHL patients(6/9 patients) developed HCV PCR reactivation. This difference between our study and other studies regarding the percentage of hepatic enzyme flare and HCV PCR reactivation can be explained by (1) difference in the definition of hepatic enzyme flare and HCV PCR reactivation between studies (2) different sample size (3) heterogeneity of the histopathology [1] (4) difference in chemotherapy regimens and the use of rituximab (5) different HCV genotype and association with other viral infection (HBV or HIV) (6) difference in duration of chronic HCV infection and the risk of developing cirrhosis.

In our study there was a significant relation between HCV reactivation and hepatic enzyme flare (p <0.001), also Parag et al. [5] agree

with our result , in contrary to Marignani et al. [13] who found no significant relation (p =0.8).

Regarding the toxicities (apart from hepatic toxicity), they were similar in all groups ; there were no statistically significant differences , with only one patient developed Grade 4 anemia in group A (the intervention arm who received ribavirin) but without significant difference

comparing to other groups (p = 0.58) . The hematologic toxicity with the use of ribavirin was to some extent accepted.

In this study the overall survival and disease-free survival in the three patients groups were comparable, although many patients among the HCV infected NHL group showed some delay in the treatment schedule, but this follow up was short.

Conclusion,

Frequency of HCV infection in patients with B cell NHL is higher than in the general population. Acute exacerbation and reactivation of chronic HCV infection occur in a sizeable subset of patients with NHL during chemotherapy.The use of ribavirin did not decrease hepatic enzyme flare or HCV PCR reactivation during chemotherapy, also ribavirin did not affect response to chemotherapy or survival rates.

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Conflicts of interest: The authors declare that there is no conflict of interest.

Ethical approval: approved.

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