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Prognostic Impact of Hepatitis C Virus Infection on Treatment Related Hepatic Toxicity and Survival of Non-Hodgkin Lymphoma Patients

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ABSTRACT

Background: The presence of Hepatitis-C Virus (HCV) infection has a great influence on Non-Hodgkin's Lymphomas (NHL) management. Previous reports showed controversy about the impact of HCV on NHL management and outcomes.

Patients and Methods: Patients with NHL diagnosed between January 2012 and December 2016 in Assiut University Hospital and South Egypt Cancer Institute were included in this analysis. Clinical features, treatment response, toxicity and outcomes of 181 patients were evaluated.

Results: HCV antibody was detected in 74 patients (40.9%) before starting treatment. HCV positive NHL patients had a higher splenic and liver involvement (p= 0.014) compared to HCV-negative patients. The most frequent histopathological type among patients was diffuse large B cell lymphoma (DLBCL). HCV-positive NHL patients had significantly higher pre-treatment AST, ALT and total bilirubin (p<0.001, <0.001 and 0.050 respectively) compared to those who were HCV negative. A significant degree of hepatic toxicity (p=0.003) and treatment interruption (p<0.001) were detected in HCV positive NHL patients during chemotherapy and/or immunotherapy. HCV had no impact on the 3-year Overall Survival (OS) and Progression Free Survival (PFS) rate (p=0.910, 0.846 respectively) of NHL patients.

Conclusions: HCV infection is associated with increased hepatic toxicity and delayed chemotherapy and had no prognostic impact on OS or PFS of NHL patients.

Key Words: *Hepatitis C virus – Non-Hodgkin lymphoma – Hepatic toxicity.*

INTRODUCTION

High prevalence of HCV infection between patients with NHL has been detected by Ferriet al in Italy and this link has been confirmed in later studies **[1,2]**. The strength of this link showed great geographic discrepancies, with higher relative risk in regions that had high HCV prevalence **[3]**. Egypt has the highest incidence of HCV infection in the world **[4]**. The optimal management of HCV positive NHL is controversial and the impact of HCV infection on treatment related hepatic toxicity and outcome of NHL patients is not clear. So in this present study, comparison between the characteristics and clinical outcome of HCV-positive and HCV-negative NHL patients were done.

PATIENTS AND METHODS

Patients:

We studied 181 NHL patients who were admitted to Assiut University Hospital and South Egypt Cancer Institute between January 2012 and December 2016.

Methods:

Serum antibodies against HCV was tested using an enzyme immunoassay (monalisa™ HCV Ag-Ab ultra assay) then confirmed by qualitative and quantitative PCR for HCV-RNA. The characteristics and clinical outcomes of 74 HCV-positive and 107 HCV-negative patients with NHL were compared. Patients who had positive hepatitis B surface antigen or antibody against human immunodeficiency virus were excluded from the study.

Liver toxicity monitoring:

For monitoring of liver toxicity, liver function tests at diagnosis, during treatment and

during follow-up periods were recorded. The definition and grades of hepatic toxicity were based on the standard National Cancer Institute-World Health Organization (NCI-WHO) common toxicity criteria grading scale (2007).

Staging, treatment and response:

Evaluation of disease stage was done according to the Ann Arbor staging system using Computed-Tomography (CT) scan and/or Positron Emission Tomography/CT (PET/CT).

- Complete Remission (CR) was defined as the disappearance of the disease in the clinical and image study;
- Partial response as >50% decrease in the largest dimension of the involved site;
- Progressive disease as >25% increase in size of involved lesions or appearance of new lesions; and
- Relapse was defined as recurrence of the disease after CR.

Treatment of lymphomas based on the histopathological type either indolent or aggressive. Younger patients with no co-morbidity received anthracycline chemotherapy regimen [CHOP ± R (rituximab ± cyclophosphamide, doxorubicin, vincristine, and prednisone)]. Older patients with co-morbidity received anthracycline free chemotherapy regimen [R ± CVP (rituximab ± cyclophosphamide, vincristine, and prednisone)].

Overall Survival (OS) is defined as the time between the date of diagnosis and last follow-up or the date of death. Progression-Free Survival (PFS) is defined as the time from the date of first line therapy until date of relapse, progression, the last follow-up or death from any cause.

Statistical analysis:

Data were described as mean ± standard deviation for numeric variables and relative frequencies for categorical variables. Comparison between groups was performed using the *t*-test, Wilcoxon Sum-Rank test and the chi-square test. Multivariate analysis was used to detect the variables associated with hepatic toxicity. The differences were considered statistically significant at $p \leq 0.05$. The survival curves were determined using the Kaplan-Meier method. The difference between groups was calculated by the Log-Rank test. Data analysis was calculated using the Statistical Package for Social Science (SPSS) Version 22.

RESULTS

Patient's baseline characteristics:

The characteristics of the patients are listed in (Tables 1,2). HCV prevalence among NHL patients was 40.9%; liver cirrhosis was detected in 23% of NHL with HCV. Males were more frequently associated with HCV infection than females (p=0.004), HCV positive NHL patients had higher splenic and liver involvement (p= 0.014) compared to HCV-negative patients. The most frequent histopathological type among NHL patients was DLBCL. There were no significant differences between the two groups as regard age, performance status, lymphoma stage, International Prognostic Index (IPI) score or type of lymphoma.

Treatment outcomes and hepatic toxicity:

Table (3) summarize chemotherapy regimens given, response to treatment, hepatic toxicity caused by treatment and the effect on treatment course modification. Regarding the chemotherapy regimens and response to treatment, there were no significant difference (p=0.088, 0.882 respectively). HCV positive NHL patients had higher pre-treatment bilirubin, AST and ALT levels (p=0.050, <0.001, <0.001 respectively). HCV positivity in NHL patients associated with significantly higher degrees of pre-treatment (p=0.017) and post-treatment liver toxicity (p=0.003). In addition, HCV-positive NHL patients more frequently had treatment delay, modification or discontinuation than HCV-negative patients (47.2% vs. 22.1%, p<0.001). On multivariate analysis only HCV infection and elevated pre-treatment bilirubin level retained their significant association with hepatotoxicity (p=0.023 and <0.001 respectively).

Survival analyses:

The mean follow-up duration was 3.75 years. There was no difference in 3-year OS between patients with or without HCV infection (75.4% vs. 71.5%, p=0.910; Fig. (1)). Neither was there significant difference in 3-year PFS [55.3% vs. 49.2%, p=0.846; Fig. (2)].

Table (1): Characteristics of NHL patients classified by HCV infection status.

Parameter	HCV positive n=74 (40.9%)	HCV negative n=107 (59.1%)	*p*-value
Age group:			
>60	24 (32.4%)	29 (27.1%)	0.439
Gender:			
Male	46 (62.2%)	43 (40.2%)	0.004
Performance stage (ECOG):			
(0-1)	55 (74.3%)	83 (77.6%)	0.614
IPI:			
L/IM.L	36 (48.6%)	63 (58.9%)	0.208
H/IM.H	38 (51.4%)	44 (41.1%)	
Liver & spleen involvement:			
Liver	2 (2.7%)	7 (6.5%)	0.014
Spleen	8 (10.8%)	11 (10.3%)	
Liver & spleen	41(55.4%)	35 (32.7%)	
Extra nodal involvement:	60 (81.1%)	79 (73.8%)	0.265
• *Ann arbor stage:*			0.235
I-11	15 (20.3%)	30 (28%)	
III-IV	59 (79.7%)	77 (72%)	
• *HCV (RNA):*			
Positive	35/36		
• *Liver cirrhosis 17/74 (23%):*			
Child-Pugh Score (A)	13 (76.5%)		
Child-Pugh Score (B)	4 (23.5%)		

ECOG : Eastern Co-Operative Oncology Group.
IPI : International Prognostic Index.

Table (2): Histopathological type of NHL patients classified by HCV infection status.

Parameter	HCV positive	HCV negative	*p*-value
Type of lymphoma:			
Indolent	26 (35.1%)	34 (31.8%)	0.637
Aggressive	48 (64.9%)	73 (68.2%)	
Diffuse large B cell lymphoma	41 (55.4%)	63 (58.9%)	
T cell lymphoma	4 (5.4%)	9 (8.4%)	
Follicular lymphoma	2 (2.7%)	5 (4.7%)	
Lymphoplasmacytic lymphoma	3 (4.1%)	3 (2.8%)	
NHL (NOS)	4 (5.4%)	9 (8.4%)	
Marginal zone lymphoma	14 (18.9%)	9 (8.4%)	
Mantle cell lymphoma	3 (4.1%)	1 (0.9%)	
Small lymphocytic lymphoma	3 (4.1%)	8 (7.5%)	

NOS: Not Other with Specified.

Table (3): Treatment outcome and hepatic toxicity in non-Hodgkin lymphoma patients classified by HCV infection status.

Variable	HCV (+) n=74 (40.9%)	HCV (–) n=107 (59.1%)	*p*-value
Anthracycline containing regimen	40 (54.1%)	70 (66.7%)	0.088
Complete remission	29 (50%)	43 (47.3%)	0.882
Bilirubin (mg/dl)	0.76±0.68	0.62±0.63	0.050
AST (u/l)	50.4±41.3	32.3±38.5	<0.001
ALT (u/l)	40.1±39.78	29.8±36.49	<0.001
Pre-treatment hepatic toxicity:			
Grade 0	43 (58.1%)	83 (77.8%)	0.017
Grade 1-2	24 (32.4%)	17 (15.9%)	
Grade 3-4	7 (9.5%)	7 (6.5%)	
Post-treatment hepatic toxicity:			
Grade 0	21 (28.4%)	64 (59.8%)	0.003
Grade 1-2	25 (33.8%)	23 (21.5%)	
Grade 3-4	28 (37.8%)	20 (18.7%)	
Interrupted treatment	34 (47.2%)	23 (22.1%)	<0.001

AST: Aspartate Aminotransferase.
ALT: Alanine Aminotransferase.

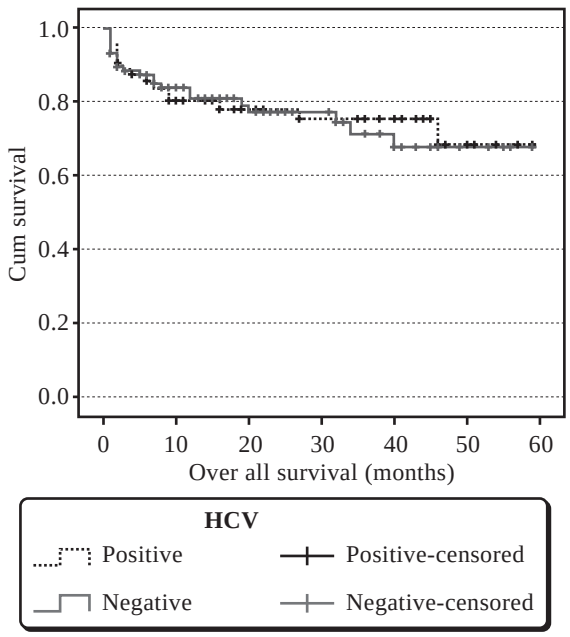

Fig. (1): Overall survival of NHL patients according to HCV status (*p*=0.910).

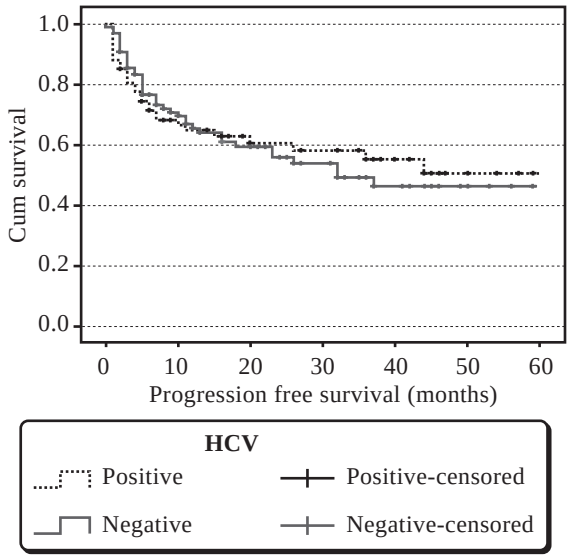

Fig. (2): PFS for patients with NHL according to HCV status (*p*-value=0.846).

DISCUSSION

The recorded prevalence of HCV infection in our study was 40.9% in NHL patients which is matched with a previous Egyptian study **[5]**. Our data matched with some reports which showed that HCV-positive patients associated with higher incidence of spleen and liver involvement **[6-8]** which was denied in other studies **[9,10]**.

In our study, HCV infection was associated with a greater incidence and severity of hepatic toxicity **[6-9,11,12]**. In agreement with our results, hepatic toxicity led to significant delay or discontinuation of chemotherapy in HCV-positive NHL patients **[6,8,13]**. In contrast, two previous studies recorded that HCV infection is not associated with increased incidence of hepatic toxicity. This might be explained by lesser degree of hepatic involvement by lymphoma and small number of HCV positive patients included in those studies **[10,14]**.

In the present study, although pre-treatment ALT and AST were higher in HCV-positive compared with HCV-negative NHL, they did not associate with hepatotoxicity in multivariate analysis. The risk factors for developing hepatotoxicity were the presence of HCV infection and pre-treatment bilirubin level. This is in agreement with Chen et al. **[9]**, who reported that HCV was the only risk factor for developing hepatotoxicity and Dlouhy et al., **[8]** who reported that elevated pre-treatment bilirubin level was a risk factor for developing hepatotoxicity.

The impact of HCV on the clinical outcome of patients with NHL is a matter of debate. In accordance with some series, the present study showed that HCV had no impact on OS or PFS **[7,9]**. However Besson et al., **[6]** reported that HCV-positive DLBCL patients had poorer overall survival but not event-free survival compared with HCV-negative patients but this study was based on a very limited number of patients and short term follow-up.

In conclusion, our study showed that HCV infection did not affect the OS or PFS of NHL patients. However, HCV increased the incidence and grades of treatment related hepatic toxicity and led to treatment modification and delay.

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