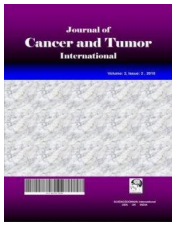

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Impact of Chronic HCV Infection on Treatment Outcome of Patients with Non-Hodgkin's Lymphoma

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Authors' contributions

This work was carried out in collaboration between all authors. Author EST designed the study, performed the statistical analysis, wrote the protocol as well as the final revised manuscript form, author EA was assigned to data analysis and interpretation of results, managed the literature searches, and wrote the first draft as well as the final revised manuscript form, authors MAS and MY shared in study design, statistical analysis, writing the protocol collection and assembly of data and managing the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Hepatitis C virus (HCV) is a hepatotropic and potentially lymphotropic virus. Chronic HCV infection might be involved in the pathogenesis of non-Hodgkin's lymphoma (NHL). Aim: to determine the prevalence of HCV infection in patients with NHL and its effect on treatment outcome. Methods: In this retrospective study, two hundred patients presented with NHL were screened for chronic HCV infection by detecting anti-HCV antibody then further confirmation with real-time polymerase chain reaction for HCV-RNA. We compared treatment response, hepatotoxicity, relapse-free survival (RFS) and overall survival (OS) according to HCV infection (NHL with negative HCV RNA group and NHL with positive HCV RNA group).
Results: Median age was 52 years old. Anti-HCV antibodies were detected in 101 patients (50.5%), and HCV-RNA was detected in 97 patients (48.5%). A curative-intent anthracycline-containing regimen as first-line treatments, with rituximab addition, was given in 68 patients. Hepatic toxicity developed in 45 patients**.** Eight patients (4%) had to discontinue chemotherapy due to severe hepatic impairment (toxicity grade 3–4). HCV infection was not a significant risk factor for

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hepatic toxicity. There was no significant difference between patients with chronic HCV infection and those without disease regarding the response to treatment. With a follow-up 12 months for patients with positive antibodies for HCV and those with negative antibodies for HCV, there was no significant difference between two the groups as regards relapse and relapse-free survival. Patients with chronic HCV infection did not have significantly different outcome than those without HCV-infection (P> 0.05).

Conclusion: HCV infection might not influence the clinical course in patients with NHL and does not affect the treatment response, patient survival and prognosis of NHL.

Keywords: Hepatitis C virus (HCV); non-Hodgkin's lymphoma (NHL); relapse-free survival (RFS); overall survival (OS).

1. INTRODUCTION

More than 180 million people are chronically infected with the hepatitis C virus (HCV) worldwide. It is a hepatotropic and potentially lymphotropic virus. HCV infection frequently lead to chronic hepatitis and is a primary cause for liver cirrhosis and its sequelae such as hepatocellular carcinoma (HCC) and haematological manifestations such as type II cryoglobulinemia or B-cell non-Hodgkin lymphoma [1].

Due to the close association between HCV and essential mixed cryoglobulinemia (EMC) which is considered an expression of a low-grade non-Hodgkin's lymphoma (NHL), it had been hypothesized that HCV might be involved in the pathogenesis of B-cell NHL [2]. A significant association between HCV and NHL has been shown in epidemiological studies in the last 20 years [3]. In the samples that taken from involved lymph nodes in B-NHL patients, HCV sequences have been identified. Various studies conducted in Eastern Europe, Egypt, Italy, Brazil, and Japan reported a high prevalence of HCV infection in B-NHL. The B-NHL development in HCV patients was at rate 2 to 4 times higher, in comparison to the general population [4-6] while other studies have not consented to this relation. In a meta-analysis conducted by Matuso et al. and included 23 case-control studies, they found that there is a healthy relationship between positive serum anti-HCV tests and NHL, especially the B-NHL type [7]. The clinical observations provided important additional evidence about the possible role of antiviral therapy for HCV infection in the treatment of patients with HCV-related low-grade (B-NHL), confirming the existence of an etiopathogenetic link [8].

2. PATIENTS AND METHODS

This retrospective study was conducted on 200 patients presented with non-Hodgkin's lymphomas, consecutively diagnosed, biopsy-confirmed and treated in the Oncology department, faculty of medicine, Menoufia University. Patients were eligible to participate if they were older than 18 years old. Patients with positive antibodies against human immunodeficiency virus (HIV) or hepatitis B surface antigen (HBsAg) were excluded. Institutional ethical board approval was taken prior to the study. Informed consent was obtained from all patients included in the study. All eligible patients were subjected to full history taking and clinical examination and routine staging procedures.

NHL was classified according to WHO classification [9]

Serological screening of HCV infection was assessed in the National Liver Institute hospital, Menoufia University: Within twenty minutes of collection, the blood was separated and the serum was divided into aliquots and stored at −80°C. Samples were later thawed and tested for anti-HCV antibody by Abbott HCV enzyme-linked immunoassay (EIA) 3.0 (Abbott Park, IL, USA) according to the manufacturer's instructions. Chronic HCV infection further confirmed with real time polymerase chain reaction for HCV-RNA (lower detection limit 15 international unit /ml). A positive result by the RT-PCR method was considered truly positive, and no further investigation was done. A sample that was negative by both RT-PCR and EIA was considered negative.

Treatment: A curative-intent anthracycline-containing regimen as first-line treatments, with rituximab addition was given in 68 patients (34%). In detail, 165 patients (82.5%) received CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone), 35 (17.5%) received CVP regimen (cyclophosphamide, vincristine and prednisone). These patients did not suffer severe hepatic function impairment or significant co-morbidities that clinically discouraged a curative approach.

Response criteria: it was relied on the revised response criteria for malignant lymphoma updated by Cheson et al. in 2007 [10].

Liver tests and assessment of liver toxicity were analyzed in all patients in the present study, pretreatment levels of alanine transaminase (ALT) and its highest levels during immunochemotherapy were collected for analysis. Definition and grading of hepatic toxicity relied on the standard National Cancer Institute-World Health Organization (NCI-WHO) common toxicity criteria grading scale [11]. Liver function tests were monitored carefully before and during immunochemotherapy, as well as during the follow-up period.

Follow-up: All patients were followed up every 3 months with laboratory tests, Computed tomography (CT) scans and/or PET/CT after the completion of immuno-chemotherapy. When relapse of lymphoma was detected using modalities and/or laboratory tests, additional chemotherapy was performed after histopathological examination.

2.1 Statistical Analysis

All data were collected, tabulated and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA) & MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Quantitative data were expressed as the mean ± SD & median (range), and qualitative data were expressed as an absolute frequencies "number" & relative frequencies (percentage). Continuous data were checked for normality by using Shapiro Walk test. Mann-Whitney U was used to compare two groups of non normally distributed data. Percent of categorical variables were compared using the Pearson's Chi-square test or Fisher's exact test when was appropriate. Trend of change in distribution of relative frequencies between ordinal data were compared using Chi-square test for trend. Relapse free survival (RFS) was calculated as the time from end of treatment to reappearance of the disease or the most recent follow-up contact in which the patient was disease free (censored). Overall Survival (OS) was calculated as the time from diagnosis to death or the most recent follow-up contact (censored). Stratification of RFS and OS was done according to HCV and hepatic toxicity. These time-to-death distributions were estimated using the method of Kaplan-Meier plot, and compared using two-sided exact log-rank test. All tests were two sided. $P < 0.05$ was considered statistically significant (S) and $p \geq 0.05$ was considered not statistically significant (NS).

3. RESULTS

3.1 Patient's Characteristics

Patient's characteristics were listed in Table 1. The median age of all patients was 52 years old (range, 18-77 years old). They were 101 males and 99 females. The patients were classified as 163 had Diffuse Large B-Cell Lymphoma (DLBCL) (81.5%) which represented the majority of the patients, 23 had follicular lymphoma (FL) (11.5%) and 14 had marginal zone lymphoma (MZL) (7.0%). By using Ann-Arbor staging system, near half of NHL cases were stage IV at time of presentation (81/200, 40.5%), with a minor proportion belonging to stage I (18/200, 9%). Advanced stage representing lumping of stage III and IV constituted 71.5% of cases. Bone marrow biopsy was positive for infiltration in 42 patients (21%). Spleen was the most frequently involved extranodal organ in 72 patients (36%), followed by the liver in 29 patients (14.5%) as shown in Table 1.

Detection of HCV antibodies and HCV RNA associated with Non-Hodgkin's lymphoma was listed in Table 1. Anti-HCV antibodies were detected by EIA in the serum of (101/200 total subjects, 50.5%) and HCV-RNA measured by RT-PCR was detected in (97/200 total subjects, 48.5%).

The prevalence of HCV-RNA measured by RT-PCR among the NHL subtypes was described in Table 2. Association with HCV infection was observed for diffuse large B cell (77/163 patients, 47.2%).

Incidence of hepatic toxicity was observed more in patients with chronic HCV infection than those without chronic HCV infection but this difference was not statistically significant. There was a significant difference between the two groups of patients regarding the grade of hepatic toxicity and effect of liver toxicity on therapeutic regimen in patients with chronic HCV infection ($p< 0.05$). Treatment was well tolerated in HCV-positive group with (79 of 97, 81.4%) patients who completed their therapeutic program without any interruption or dosage reduction in comparison to (99 of 103, 96.1%) in HCV- negative group.

Table 1. Clinical, laboratory and imaging characteristics of 200 NHL patients

Variable	Number	%
Sex		
Male	101	50.5%
Female	99	49.5%
Age (years old),median (range)	52 (18 – 77)	
Histology		
DLBCL	163	81.5%
FL	23	11.5%
MZL	14	7%
Stage		
Stage I	18	9%
Stage II	39	19.5%
Stage III	62	31%
Stage IV	81	40.5%
B symptoms		
Absent	135	67.5%
Present	65	32.5%
Bulky lymph nodes		
Absent	168	84%
Present	32	16%
Lactate dehydrogenase		
Normal	84	42%
Elevated	116	58%
Bone Marrow infiltration		
Absent	158	79%
Present	42	21%
Spleen involvement		
Absent	128	64%
Present	72	36%
Liver involvement		
Absent	171	85.5%
Present	29	14.5%
Other extranodal		
Not involved	126	63%
Involved	74	37%
GIT	21	10.5%
Lung	13	6.5%
Skin	10	5%
Other	30	15%
Porta hepatis node involvement		
Absent	189	94.5%
Present	11	5.5%
HCV infection		
Anti- HCV antibody		
Negative	99	49.5%
Positive	101	50.5%
HCV-RNA		
Negative	103	51.5%
Positive	97	48.5%
Treatment		
Modality		
Chemotherapy	132	66%
Chemotherapy & rituximab	68	34%
HCV-RNA Chemotherapy		
CVP	35	17.5%
CHOP	165	82.5%

DLBCL= Diffuse Large B-cell Lymphoma, FL= Follicular Lymphoma, MZL= Marginal zone lymphoma, GIT= Gastrointestinal tract

Table 2. Detection of HCV RNA in patients with major NHL subtypes

	NHL with negative HCV-RNA		NHL with positive HCV-RNA		Total	
Histology	No.	%	No.	%	No	%
DLBCL	86	52.8%	77	47.2%	163	100%
FL	10	43.5%	13	56.5%	23	100%
MZL	7	50%	7	50%	14	100%

DLBCL= Diffuse Large B-cell Lymphoma FL= Follicular Lymphoma MZL= Marginal zone lymphoma

Seven of 97 (7.2%) patients had to discontinue chemotherapy due to severe hepatic function impairment (toxicity grade 3–4) in HCV-positive group in comparison to (3 of 103, 2.9%) in HCV-negative group as shown in Table 3.

There was no significant difference between HCV negative group and HCV positive group (Table 4) as regards the response to treatment (p=0.916). As regards mortality & overall survival (OS), there was no significant difference between HCV negative group and HCV positive group (Table 4 & Fig. 1) (the 1-year OS, 93.7 % versus 95.4%, p=0.546).

There was no significant difference was found between HCV-positive group (with or without hepatitic toxicity) and HCV- negative group (with or without hepatitic toxicity) regarding mortality (p=0.144) and overall survival (p=0.138).

There was no significant relation between treatment and hepatic toxicity, regardless of the regimen that was administered. The addition of rituximab to chemotherapy regimens had a non-significant relation with hepatic toxicity (18.9% with CHOP vs. 26.0%with R-CHOP; (p> 0.05).

With a follow-up of 12 months, five patients relapsed. Relapse free survival (RFS) rate was 96.7%. There was no significant difference between HCV negative group and HCV positive group (Table 5 & Fig. 2) as regards relapse and relapse free survival.

4. DISCUSSION

We have compared the prevalence of HCV infection in our study population with that of the general population of Egypt, where a large, epidemiological study had demonstrated a prevalence of 14.7% of HCV infection [12]. The principal finding of the current study is a positive association of HCV infection with NHL While our finding of a significant association between HCV infection and B cell lymphoma was consistent with the results of several European, American and korean studies, it was contradicted by others, Gisbert and his coworkers observed that the mean prevalence of HCV infection calculated from 5632 patients in 50 studies included in systematic review and meta-analysis was approximately 15% [13] Subsequently, in 2006, a meta-analysis of 15 case-control studies on the association between HCV infection and NHL demonstrated a pooled relative risk of lymphoma of (OR = 2.5, 95% CI 2.1–3.1) among HCV-positive subjects [14]. A high prevalence of HCV infection in NHL patients has been shown to exist in many geographical areas of high HCV prevalence such as Brazil, Italy [15]. In Egypt, where the virus is highly endemic, Cowgill and his coworkers reported a positive association of current HCV infection with increased risk of B-cell NHL as a whole (OR = 2.3, 95% CI 1.5–3.5) [16]. In contrast, several studies did not support an association of HCV with NHL. Franceschi and his coworkers, according to the EPIC study, reported that there was no evidence of an association between HCV and NHL [17]. A study in Denmark, which is an area of low HCV prevalence, has shown association of HCV and lymphoma [18]. These differences seem to be largely geographical-based. At the same time, different results were reported even in studies performed within the same country. These contradictory results suggest that there are other factors (genetic, environmental and others) that may have to be present in combination with HCV to trigger B-cell expansion into a NHL [13].

In this study, diffuse large-cell histology was the dominant subtype followed by the follicular subtype and MZL in serum positive patients (79.4%, 13.4% and 7.2%) and also in serum negative patients (83.5%, 9.7% and 7.2%) respectively. These findings were similar to a study from the United States which reported that the most common HCV related B-NHLs was diffuse large B-cell lymphoma (DLBCL) (62%), followed by follicular lymphoma (13%) and marginal zone lymphoma (MZL) (11%) [19]. Similar finding was reported by Gouda et al. who observed that the dominant subtype in HCV-RNA

Table 3. Comparison between HCV negative group and HCV positive group as regards hepatic toxicity of treatment

Hepatic toxicity of treatment	NHL with negative HCV RNA (N=103)		NHL with positive HCV RNA (N=97)		Test	p-value
	No.	%	No.	%		
AST (U/L)						
Grade 0	88	85.4%	69	71.1%	8.958	0.003
Grade 1	12	11.7%	16	16.5%		
Grade 2	3	2.9%	7	7.2%		
Grade 3	0	0%	4	4.1%		
Grade 4	0	0%	1	1%		
ALT (U/L)						
Grade 0	86	83.5%	62	63.9%	10.203	0.001
Grade 1	7	6.8%	15	15.5%		
Grade 2	8	7.8%	9	9.3%		
Grade 3	2	1.9%	8	8.2%		
Grade 4	0	0%	3	3.1%		
Direct serum bilirubin (mg/dl)						
Grade 0	92	89.3%	75	77.3%	7.952	0.005
Grade 1	9	8.7%	11	11.3%		
Grade 2	2	1.9%	8	8.2%		
Grade 3	0	0%	3	3.1%		
Serum albumin (g/dl)						
Grade 0	101	98.1%	82	84.5%	11.391	0.001
Grade 1	2	1.9%	13	13.4%		
Grade 2	0	0%	2	2.1%		
Alkaline phosphatase (U/L)						
Grade 0	93	90.3%	82	84.5%	0.778	0.378
Grade 1	8	7.8%	14	14.4%		
Grade 2	2	1.9%	1	1%		
Hepatic toxicity						
Not occurred	85	82.5%	70	72.2%	2.140	0.076
Occurred	18	17.5%	27	27.8%		
Grade						
Grade 0	85	82.5%	70	72.2%	5.933	0.015
Grade 1	8	7.8%	8	8.2%		
Grade 2	8	7.8%	9	9.3%		
Grade 3	2	1.9%	6	6.2%		
Grade 4	0	0%	4	4.1%		
Effect of liver toxicity on treatment						
No effect	99	96.1%	79	81.4%	11.083	0.001
Prolongation of intervals	3	2.9%	11	11.3%		
Discontinue chemotherapy	1	1%	7	7.2%		

positive patients was DLBCL followed by follicular lymphoma (72% and 18%) [20]. In contrast, The B-NHL subtype commonly reported in European and Japanese studies were MZL, particularly splenic zone lymphoma (SMZL), lymphoplasmacytic lymphoma (LPL) and DLBCL [21,22]. The International Lymphoma Epidemiology Consortium (InterLymph) study reported pooled results of HCV related B-NHL from a large international multicenter data source. The study included 11,053 participants, 4,784 cases, and 6,269 controls from seven case-control studies conducted in the United States, Europe and Australia with information on HCV infection. HCV infection was detected in 172 NHL cases (3.6%) and in 169 (2.7%) controls. In subtype-specific analyses, HCV prevalence was associated with marginal zone lymphoma, diffuse large B-cell lymphoma, and lymphoplasmacytic lymphoma. Notably, risk estimates were not increased for follicular lymphoma [4]. Goldman and his coworkers, in a

Table 4. Comparison between HCV negative group and HCV positive group as regards response to treatment, mortality and overall survival

Response to treatment	NHL with negative HCV RNA (N=103)		NHL with positive HCV RNA (N=97)		NHL patients Total (N=200)		Test	p-value
	No.	%	No.	%	No.	%		
CR	66	64.1%	64	66%	130	65%	0.011	0.916
PR	22	21.4%	18	18.6%	40	20%		
OAR	88	85.4%	82	84.5%	170	85%		
SD	5	4.9%	6	6.2%	11	5.5%		
PD	10	9.7%	9	9.3%	19	9.5%		
Alive	91	88.3%	89	91.8%	180	90%	0.643	0.423
Died	12	11.7%	8	8.2%	20	10%		
12 month Overall survival	93.7%		95.4%				0.364	0.546

CR= Complete remission PR= Partial remission OAR= Overall response
SD= Stable disease PD= Progressive disease

Table 5. Comparison between HCV negative group and HCV positive group as regards relapse & relapse free survival

Variables	NHL with negative HCV RNA (N=66)		NHL with positive HCV RNA (N=64)		Test	P value
Relapse						
Not occurred	64	97%	61	95.3%	0.241	0.623
Occurred	2	3%	3	4.7%		
Relapse free survival						
12 month RFS	96.8%		96.7%		0.001	0.978

study among the largest investigations of HCV and NHL and its subtypes to date in Egypt. The results suggested that HCV infections are associated with diffuse large B cell, marginal zone, and follicular B-cell lymphomas, respectively [23].

Indolent and aggressive non-Hodgkin's B-cell lymphoma patients are commonly treated with immunochemotherapy programs which contain rituximab, cytotoxic drugs, and corticosteroids. In patients carrying HCV infection, these types of treatment can increase the risk of subsequent liver damage and HCV-related hepatotoxicity could hamper application of adequate treatment [24].

In the current study, there was no significant relation between HCV infection and response to treatment. Complete response was 66% and 64.1% in HCV positive and HCV-negative patients, respectively that came in agreement with Nishikawa et al. [25]. This study showed that prognosis did not differ according to HCV infection. The median follow-up was 12 months for patients who were HCV-positive and HCV-negative, respectively. HCV infection was not a significant risk factor for prognosis (overall survival, 93.7% vs. 95.4%, P > 0.05). Incidence of hepatic toxicity observed more in patients with HCV infection but that was not statistically significant as of the 97 patients who were HCV-positive, 26 (26.8%) had hepatic toxicity, compared with 16.5% of those who were HCV-negative. In sharp contrast, the incidence of severe hepatic toxicity grade (3-4) was higher in HCV-positive patients. These findings were consistent with that reported by Ennishi and his coworkers [26]. There was statistically a high significant relation between hepatic toxicity and response to treatment (P<0.001). However, hepatic toxicity was not associated with poor overall survival in patients who were positive for HCV RNA. There was no significant relation was found between treatment and hepatic toxicity, regardless of the regimen that was administered. The addition of rituximab to chemotherapy regimens had a non-significant relation with hepatic toxicity. The use of rituximab was not associated with increased rate of severe hepatotoxicity. That was similar to the study by Ennishi et al. on 131 HCV-positive patients and 422 of whom were HCV-negative treated with R-CHOP that reported a similar outcome in HCV-positive patients compared to HCV-negative group [26]. Abu-Taleb et al.

concluded that HCV-positive patients with DLBCL treated with rituximab plus CHOP have high incidence in hepatic toxicity [27]. The outcome of patients treated with R-CHOP in the study by Merli (3-year OS 71%) was similar to that reported by Ennishi, In Merli study, 535 consecutive cases with HCV associated DLBCL treated by anthracycline based chemotherapy have been evaluated. Severe hepatotoxicity has been observed in 14% of the cases and did not record any difference in terms of severe hepatotoxicity between the patients treated with R-CHOP and those treated with CHOP [28]. The outcome of HCV-positive DLBCL has been shown to be similar to that of their HCV-negative counterpart once patients receive adequate treatment. However, this issue is still a matter of debate [29].

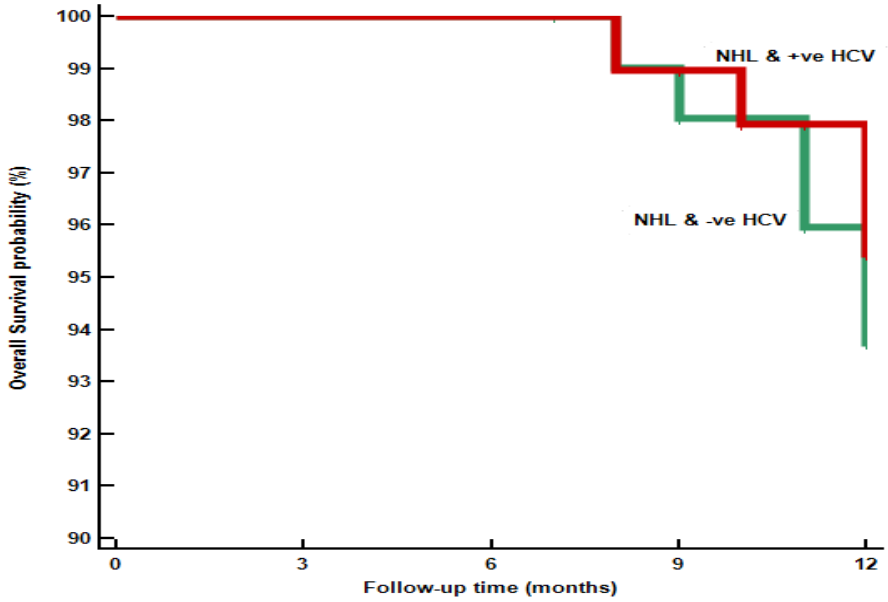

Fig. 1. Kaplan Meier plot of overall survival stratified by HCV

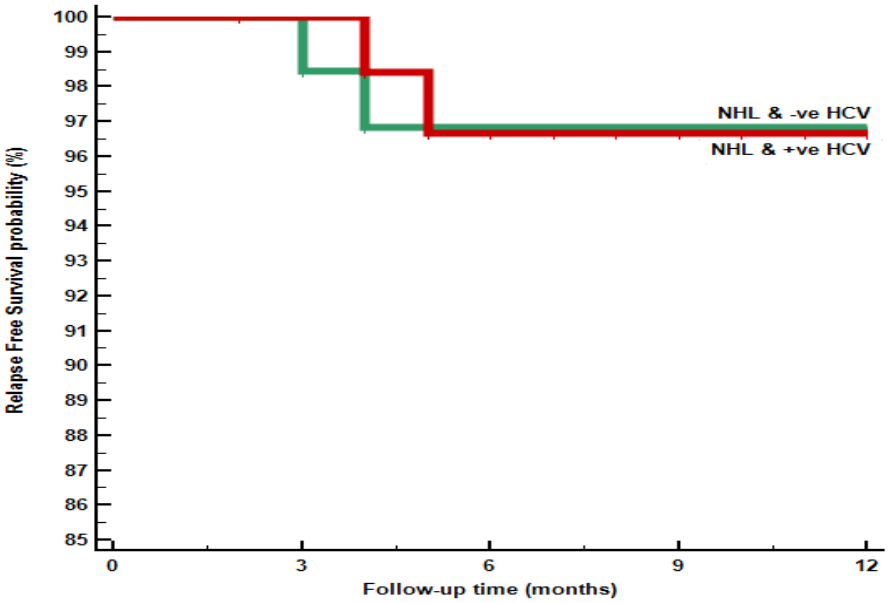

Fig. 2. Kaplan Meier plot of relapse free survival stratified by HCV

In the pre-rituximab era, few studies evaluated the clinical outcome of HCV-positive DLBCL. In a retrospective analysis from GELA studies (LNH 93and LNH 98) the outcome of the patients with HCV has been found to be poor. The short term hepatic toxicity has been found to be strongly increased and has been found in 15 of the 23 cases [30]. Zaky and his coworkers analyzed 137 cases with HCV positive DLBCL and compared the outcome of the patients treated with chemotherapy with or without rituximab. They found significantly increased hepatictoxicity (28% vs. 18%) receiving rituximab and worse outcome for progression free survival (PFS) and OS [31]. However, all of these studies are retrospective, sample sizes are relatively small and rituximab using is not balanced in study groups and also late complications associated with rituximab in these cases are not clear due to the limited time of follow ups. In a prospective study from Egypt, Salah-Eldin and his coworkers found no significant difference for PFS and OS according to the rituximab administration. This study was carried out on 280 HCV positive cases with DLBCL; 200 of them received immunochemotherapy while 80 cases received chemotherapy only. Severe hepatic toxicity was observed in 26.5% of the cases treated by using rituximab although severe hepatotoxicity developed in 13.75% of the cases not receiving rituximab [32].

5. CONCLUSION

Our results confirmed that there is a clear association between chronic HCV infection and B- NHL. HCV infection seemes not to affect significantly the response to treatment outcome, patient survival and prognosis of NHL. Our results highlighted a higher incidence of severe hepatic toxicity grade (3-4) in patients who were HCV-positive that could lead to discontinue chemotherapy or required prolongation of intervals between chemotherapy cycles, or reduction of scheduled dosage. HCV-positive patients who develop severe hepatic toxicity showed significantly less response to the treatment used in NHL.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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