Research Article

Impact of Immunochemotherapy-Related Hepatic Toxicity on the Outcome of HCV-Positive Diffuse Large B-Cell Lymphoma Patients

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We conducted this prospective study which included 28 de novo CD20-positive DLBCL patients to assess the clinical outcome, treatment response, and hepatic toxicity in DLBCL patients who received rituximab-CHOP as a first line treatment in relation to HCV infection status. We included 7 patients with positive HCV infection (group A) and 21 patients with negative HCV infection (group B). HCV infection was not a significant risk factor for prognosis (1-year event-free survival rates, 71.4% versus 81%, $P = 0.53$; overall survival rates, 85.7% versus 90.5%, $P = 0.72$, for groups A and B, resp.). CR rate was 71.4% (5/7) in group A and 76.2% (16/21) in group B ($P = 0.8$). Of the 7 patients who were HCV positive, 2 (28.6%) had enzyme flare (grade 2), compared with 1 of the 21 (4.8%) patients who were HCV negative ($P = 0.15$). Two (28.6%) of the 7 positive HCV infection patients had viral reactivation ($\geq 1 \log_{10}$ IU/mL increase in the viral load). No patient required discontinuation of immunochemotherapy owing to hepatotoxicity in either group. In conclusion, HCV infection might not influence the clinical course in DLBCL patients who receive rituximab-CHOP. Close monitoring of hepatic function and viral load is recommended.

1. Introduction

The role of HCV infection in lymphomagenesis is related to several mechanisms such as the sustained antigenic stimulation of the B-cell compartment, viral lymphotropism, and viral proteins, chromosomal aberrations, cytokines, and microRNAs [1].

For decades, the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was the standard regimen for patients with DLBCL, curing about 30% of the patients; no advantage was observed with more intensive combinations [2]. However, the addition of rituximab, a chimeric monoclonal antibody which targets CD20-positive lymphocytes, to the CHOP regimen induces a significantly higher complete-response rate and increased event-free and overall survival in patients with DLBCL. Therefore, rituximab-combined CHOP regimen (R-CHOP) as

immunochemotherapy is now considered to be the standard treatment for patients with DLBCL [3].

Although hepatitis B virus (HBV) reactivation is a well-documented and potentially fatal complication that occurs frequently after introduction of rituximab, data on HCV reactivation or liver dysfunction after chemotherapy for NHL especially with rituximab-containing regimen are controversial [4].

In this report, we compare the clinical characteristics, treatment-related toxicity, and outcome of our patients in relation to HCV status.

2. Patients and Methods

2.1. Eligibility. This prospective study included twenty-eight patients with pathological proof of CD20-positive DLBCL. On the basis of statistical theory we collected up to 7 patients

with HCV-positive infection (group A) and 21 patients with HCV-negative infection (group B). All of them had detectable HCV RNA before treatment and none had received previous treatment for HCV infection at Medical Oncology Department, Zagazig University Hospitals, during the period from February 2013 to October 2014.

Patients were excluded if they were positive for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), or human immunodeficiency virus. Patients with primary central nervous system lymphoma and primary testicular lymphoma were also excluded.

All eligible patients were treated with rituximab-CHOP, on day 1 of a 21-day cycle with intravenous rituximab 375 mg/m²; cyclophosphamide, 750 mg/m²; doxorubicin, 50 mg/m²; vincristine, 1.4 mg/m² (maximum of 2.0 mg); and prednisone, 100 mg by mouth daily for 5 days. Patients with stage I, stage IE, or nonbulky stage II were treated with three cycles of CHT followed by involved field radiotherapy beginning 3 weeks after the third cycle of chemotherapy. Patients with more advanced disease received a minimum of six cycles of chemotherapy or two cycles beyond documentation of complete remission. Treatment was stopped if there was no response, if the lymphoma progressed, or if severe adverse effect developed.

2.2. Liver Function Tests and HCV Viral Markers. In all patients enrolled, the pretreatment levels of alanine aminotransferase (ALT) as well as its highest levels during treatment and its level at the last follow-up after completing treatment were collected.

In HCV-positive patients, HCV RNA in serum was done at the beginning and at the end of treatment as well as to patients who developed enzyme flare during the course of treatment. 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 and patients with detectable HCV RNA in serum were considered to have proven HCV infection [5].

Acute exacerbation of chronic HCV infection (enzyme flare) was defined as a 3-fold or greater increase in serum ALT level above the upper limits of normal (ULN = 40 IU/L), in the absence of use of hepatotoxic drugs (other than chemotherapeutics), or other systemic infections besides HCV.

HCV reactivation (viral flare) 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.

3. Toxicity Evaluation

Toxicities were assessed according to the *National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.3 2010*.

4. Follow-Up

At the end of therapy, clinical examination and laboratory investigations (including LFTs) were done every 3 months and radiological evaluation by computed tomography scan was done every 6 months till the end of the study.

This study was approved by the Institutional Review Board of Zagazig University with all of the provisions of the Declaration of Helsinki with informed consent from all patients.

5. Statistical Analysis

The collected data were presented, summarized, tabulated, and analyzed by using computerized statistical packages (SPSS version 20). Mean $\pm$ standard deviation with median and range when appropriate described quantitative data. Numbers with percentages described qualitative data. Chi-square test (χ^2) and Fisher exact test were used to compare proportions while independent sample *t*-test was used to compare means between both groups and paired sample *t*-test to compare the changes in viral load before and after treatment (*P* value ≤ 0.05 was considered to be statistically significant at 95% confidence interval).

5.1. Survival Analysis. Kaplan and Meier method was used to estimate overall and event-free survival and log rank test compared survival curves (*P* value was considered significant at ≤ 0.05 levels). *Overall survival (OS)* was calculated as the interval between the date of diagnosis till date of death or date of last follow-up. *Event-free survival (EFS)* was calculated from the treatment initiation date till the date of documented disease progression, relapse, or the end date of the study.

6. Results

6.1. Patient Characteristics. A total of 28 patients with CD20-positive DLBCL were enrolled in our study. Pretreatment characteristics are shown in Table 1.

The study included 18 males (64.3%) and 10 females (35.7%) with a ratio of 1.8 : 1 and the median age of the patients at presentation was 49 years (range: 19–73 years). Seven (25%) out of the 28 patients were positive for HCV antibody and had detectable HCV RNA before chemotherapy.

At presentation, 57.1% of patients (16/28 of patients) had B symptoms and 39.3% of patients (11/28 of patients) presented with splenomegaly while 46.4% of patients (13/28 of patients) had hepatomegaly.

In addition, 10.7% of patients (3/28 of patients) had splenic involvement while only 3.6% of patients (1/28 of patients) had hepatic involvement at presentation.

Extranodal involvement was found in 25% of patients (7/28 patients): four of them presented with single extranodal site while three presented with 2 extranodal sites.

Elevated serum level of LDH was found in 67.9% of patients (19/28 patients) and 64.3% of patients (18/28

TABLE 1: The baseline characteristics of patients of both groups.

Variable	HCV positive (group A; n = 7) Number (%)	HCV negative (group B; n = 21) Number (%)	P value
Age (years)			
Median (range)	49 (34–66)	49 (19–73)	0.58
Gender			
(i) Male	5 (71.4%)	13 (61.9%)	0.65
(ii) Female	2 (28.6%)	8 (38.1%)	
B symptoms	5 (71.4%)	11 (52.4%)	0.66
Performance status			
(i) 0-1	6 (85.7%)	12 (57.1%)	0.36
(ii) >1	1 (14.3%)	9 (42.9%)	
Elevated LDH	5 (71.4%)	14 (66.7%)	0.82
DLBCL stage			
(i) I	0 (0%)	3 (14.3%)	0.67
(ii) II	3 (42.9%)	9 (42.9%)	
(iii) III	3 (42.9%)	6 (28.5%)	
(iv) IV	1 (14.2%)	3 (14.3%)	
BM involvement	1 (14.3%)	1 (4.8%)	0.44
Splenomegaly (only)	3 (42.9%)	8 (38.1%)	0.82
Splenic involvement	3 (42.9%)	0 (0%)	0.01*
Hepatomegaly (only)	3 (42.9%)	10 (47.6%)	0.82
Hepatic involvement	0 (0%)	1 (4.8%)	0.56
Extranodal sites			
(i) 1	0 (0%)	4 (14.3%)	0.64
(ii) 2	1 (14.3%)	2 (9.5%)	
R-IPI			
(i) Very good	0 (0%)	7 (33.3%)	0.19
(ii) Good	6 (85.7%)	11 (52.4%)	
(iii) Poor	1 (14.3%)	3 (14.3%)	

* means significant ($P < 0.05$).

patients) had a PS ≤ 1 , while 46.4% of patients (13/28 patients) presented with advanced stages (III and IV).

Regarding the R-IPI, 25% of patients (7/28 patients) had very good score while 60.7% of patients (17/28 patients) had good score and only 14.3% of patients (4/28 patients) had poor score.

There was a significant difference as regards the splenic involvement as 42.9% of patients in group A (3/7 patients) versus no patients in group B presented with splenic involvement ($P = 0.01$).

However, there was no significant difference between both groups as regards the age, gender, B symptoms, PS, stage, pretreatment LDH, extranodal sites, splenomegaly, hepatomegaly, hepatic involvement, and bone marrow involvement.

The baseline pretreatment laboratory characteristics of both groups; there was a significant difference as regards the

TABLE 2: The baseline laboratory values of both groups.

Variable	HCV positive (group A) Mean $\pm$ standard deviation	HCV negative (group B) Mean $\pm$ standard deviation	P value
WBC (cells/mm ³)	6.3 $\pm$ 2.1	6.2 $\pm$ 2.7	0.95
Hemoglobin (g/dL)	12.6 $\pm$ 0.8	11.2 $\pm$ 1.5	0.03*
Platelets ($\times 10^3$ /mm ³)	276.9 $\pm$ 115.4	276.7 $\pm$ 104.3	0.99
Bilirubin (mg/dL)	0.9 $\pm$ 0.5	0.8 $\pm$ 0.2	0.48
Albumin (mg/dL)	4.0 $\pm$ 0.5	4.1 $\pm$ 0.4	0.49
ALT (IU/L)	55.0 $\pm$ 30	37.1 $\pm$ 15	0.14
AST (IU/L)	56.3 $\pm$ 30	40.6 $\pm$ 17	0.1
INR	1.2 $\pm$ 0.3	1.1 $\pm$ 0.2	0.23
Creatinine (mg/dL)	0.7 $\pm$ 0.1	0.8 $\pm$ 0.3	0.51

* means significant ($P < 0.05$).

baseline hemoglobin level ($P = 0.03$). However, no significant differences were found between both groups regarding the pretreatment WBCs, platelets, serum bilirubin, ALT, AST, INR, albumin, and serum creatinine (Table 2).

7. Response to Chemotherapy

Responders (who achieved CR) were 71.4% of group A (5/7 patients) compared to 76.2% of group B (16/21 patients), while nonresponders (who achieved PR, PD, or SD) were 28.6% of group A (2/7 patients) compared to 23.8% of group B (5/21 patients). However, no significant difference was found as regards the response to chemotherapy between the two groups ($P = 0.8$).

7.1. Overall Survival. After a median follow-up period of 18.1 months (range, 6.1–20.1 months), 10.7% of patients died (3/28 patients); the 1st was HCV-negative and achieved PR and then died following coronary bypass surgery after 7 months of diagnosis, the 2nd patient was HCV positive and achieved PR and then died when shifted to a salvage therapy due to progression of lymphoma and development of hepatic failure after 8 months of diagnosis, and the third patient was HCV-negative and achieved PR and died due to disease progression at 11 months of diagnosis.

The 1-year overall survival rate was 89.3% with a mean of 18.7 ± 0.69 months (95% CI; 17.4–20.1 months); however, the median OS was not reached.

The 1-year event-free survival rate was 78.6% with a mean of 17.7 ± 0.87 months (95% CI; 15.9–19.3 months) while the median EFS was not reached.

Patients with HCV-positive infection did not have significantly different outcome than those with HCV-negative

FIGURE 1: Overall survival in relation to HCV infection.

FIGURE 2: Event-free survival in relation to HCV infection.

infection, (the 1-year OS, 85.7% versus 90.5%, $P = 0.72$) and (the 1-year EFS, 74.1% versus 81%, $P = 0.53$; Figures 1 and 2, resp.).

8. Hepatic Toxicity

8.1. Changes in the ALT Levels. As shown in Table 2, the pre-treatment transaminase levels were not significantly different between the two groups.

Among the HCV-infected subjects, the incidence of hepatitis flares (defined as an ALT increase >3 times the upper limit of normal (grade 2)) was 28.6% (2/7 patients) versus 4.8% (1/21 patients) among the HCV-uninfected individuals. However, no patient developed grade 3 or grade 4 elevation of in ALT in both groups ($P = 0.15$).

The onset of enzyme flare in group B started at the 6th cycle of R-CHOP while, in group A, it occurred at the 2nd and 3rd cycles in the 2 patients who developed enzyme flare (Figure 3). Liver damage did not result in treatment discontinuation in any of them.

8.2. HCV Reactivation. Within the HCV-positive group, the median pretreatment HCV viral load was 320,400 IU/mL (34,500–2,360,000 IU/mL) while the median level after treatment was 970,821 IU/mL (79,236–5,420,000 IU/mL; $P = 0.049$).

Viral reactivation (>1log₁₀ increase in the viral load) occurred in (28.6%; 2/7 patients) in group A and was associated with grade 2 increase in the ALT level (enzyme flare)

FIGURE 3: Changes in ALT levels in patients who developed enzyme flare.

in one patient of them. However, one patient within the same group developed enzyme flare but without viral reactivation. Thus, there was no significant difference regarding the development of enzyme flare in respect to viral reactivation ($P = 0.43$; Tables 3 and 4).

One of the 2 patients who had viral reactivation HCV load was improved after the treatment had been finished while the other one died without reevaluation of his HCV load.

TABLE 3: Hepatic toxicity in both groups.

	Grade	HCV positive (group A; n = 7)	HCV negative (group B; n = 21)	P value
ALT	G 0	1 (14.3%)	9 (42.8%)	0.15
	G 1	4 (57.1%)	11 (52.4%)	
	G 2	2 (28.6%)	1 (4.8%)	
AST	G 0	1 (14.3%)	12 (57.1%)	0.07
	G 1	4 (57.1%)	8 (38.1%)	
	G 2	2 (28.6%)	1 (4.8%)	
Bilirubin	G 0	5 (71.4%)	21 (100%)	0.06
	G 1	1 (14.3%)	0 (0%)	
	G 2	1 (14.3%)	0 (0%)	
INR	G 0	4 (57.1%)	20 (95.2%)	0.04*
	G 1	3 (42.9%)	1 (4.8%)	
Albumin	G 0	6 (85.7%)	21 (100%)	0.25
	G 1	0 (0%)	0 (0%)	
	G 2	1 (14.3%)	0 (0%)	
Alkaline phosphatase	G 0	3 (42.9%)	14 (66.7%)	0.21
	G 1	3 (42.9%)	7 (33.3%)	
	G 2	1 (14.3%)	0 (0%)	
Hepatic failure [#]	G 0	6 (85.7%)		0.25
	G 3	0 (0%)		
	G 4	1 (14.3%)		

* means significant ($P < 0.05$).

[#] means hepatic encephalopathy.

TABLE 4: The relationship between development of enzyme flare and viral reactivation.

Development of enzyme flare	Viral reactivation (n = 2)	No viral reactivation (n = 5)	P value
(i) Yes	1 (50%)	1 (20%)	0.43
(ii) No	1 (50%)	4 (80%)	

The details of enzyme and viral reactivation in addition to the outcome of HCV-positive patients are shown in Table 5.

8.3. Other Hepatic Toxicities. Grade 1 elevation of INR was significantly higher in group A while no significant differences were found between both groups as regards the changes in the serum albumin, alkaline phosphatase, bilirubin, or development of hepatic encephalopathy (Table 3).

Response rate was significantly higher in patients with normal baseline LDH and very good R-IPI score ($P = 0.01$ and 0.001 , resp.).

The 1-year OS rate was significantly higher in responders compared to the nonresponders (100% versus 57.5%; $P = 0.001$). However, no significant relation between OS and enzyme flare and delayed scheduled therapy (92% versus 66.7%; $P = 0.17$ and 94.4% versus 81.8%; $P = 0.29$, resp.).

Moreover, the 1-year EFS rate was significantly worse in those who developed enzyme flare and delayed the scheduled therapy (84% versus 33.3%; $P = 0.01$ and 94.1% versus 54.5%; $P = 0.04$, resp.).

Regarding the R-IPI score, the EFS was better in favorable patients as follows: (100%) for very good versus (82.4%) for good versus (25%) for poor score; $P = 0.006$; also a significant difference was found as regards the OS in relation to the R-IPI (100%, 94.1%, and 50% for very good, good, and poor scores, resp.; $P = 0.025$).

9. Discussion

In our study, we compared clinical outcome, treatment response, and hepatotoxicity in patients with DLBCL who received R-CHOP in respect to HCV infection.

Considerable percentage of patients presented with splenomegaly most probably due to endemicity of schistosomiasis in our geographic region. However, splenic involvement was found only among HCV-positive patients compared to HCV-negative patients (42.9% versus zero%; $P = 0.01$) which is similar to reports of Nishikawa et al. [6], Ennishi et al. [7], Besson et al. [8], and Visco et al. [9] where splenic involvement was 30.2%, 18%, 46%, and 34%, respectively, in HCV-positive patients. HCV-negative patients showed significantly lower mean hemoglobin level at presentation than HCV-positive patients ($P = 0.03$) unlike results of Nishikawa et al. [6].

In the present study, favorable objective response to R-CHOP was obtained in the HCV group as compared with some previous reports [6, 7, 10], and there was no significant difference between the HCV group and the HCV-negative group in terms of CR that comes in agreement with Nishikawa et al. [6] and Ennishi et al. [7], suggesting that the addition of rituximab did not seem to affect the treatment response of DLBCL patients with HCV infection.

In terms of OS and EFS, there were no significant differences between both groups in the present study. Our results suggested that, in DLBCL patients, HCV infection was not a significant risk factor for prognosis in patients receiving R-CHOP.

Poor RIPI, enzyme flare, and treatment delay had significant influence on EFS ($P = 0.006$, 0.011 , and 0.012 , resp.), but regarding OS only poor RIPI had significant effect ($P = 0.025$).

In the present study, the pretreatment ALT levels were not significantly different regarding HCV infection ($P = 0.15$) which was similar to other previous reports [6, 7]. However, our results showed no significant difference for development of hepatotoxicity (enzyme flare) as a result of higher basal ALT ($P = 0.54$) which was consistent with Visco et al. [9] who also reported no association between the initial severity of hepatic disease and subsequent liver drug toxicity, regardless of the regimen that was administered, but was inconsistent with [6, 7] which reported that hepatotoxicity in HCV-positive DLBCL patients undergoing immunochemotherapy was more likely to occur if pretreatment ALT levels were high. Our results demonstrate a good tolerance to R-CHOP in HCV-infected DLBCL patients; as no significant difference in enzyme flare developed during treatment between both groups this comes in agreement with Nishikawa et al. [6], who reported that enzyme flare was

TABLE 5: Details and outcome of HCV-positive patients.

Patient	Child*	R-IP†	HPs‡	Baseline before RCHOP		During RCHOP		Hepatic toxicity		Last follow-up after RCHOP		Viral reactivation (≥1 log ₁₀ over the baseline)	Response	Outcome/OS (months)	
				ALT# (U/L)	HCV-RNA (IU/mL)	ALT peak	Cycle	Grade (ALT > 3ULN)	Enzyme flare Onset from initiation of R-CHOP (days)	HCV-RNA during flare	ALT				HCV-RNA
1	A5	G	I	30	2,360,000	40	7th	0	No	—	25	5,420,000	No	CR	Alive/19
2	A5	G	L	26	814,800	60	3rd	1	No	—	20	630,250	No	CR	Alive/17
3	A6	G	L	30	34,500	48	4th	1	No	—	26	3,671,000	Yes	CR	Alive/20
4	A5	G	I	75	320,400	80	5th	1	No	—	60	970,821	No	CR	Alive/19
5	A5	G	I	99	2,172,650	112	5th	1	No	—	40	4,972,532	No	CR	Alive/18
6	A5	G	L	71	127,835	132	2nd	2	Yes	28	20	639,015	No	PR	Alive/18
7	A6	P	H	54	92,628	124	4th	2	Yes	94	28	79,236	Yes	PR	Died/7.8

* Child classification (A5-6 = well-compensated disease). † R-IP score (G = good, P = poor outcome). ‡ HPS = HCV prognostic score differentiating between three risk categories (L = low, I = intermediate, and H = high). § The ALT ULN = 40 IU/L.

15.9% in HCV-negative versus 25% in HCV-positive; $P = 0.28$. On the contrary, Ennishi et al. [7] reported that enzyme flare was significantly higher in HCV-positive patients who received immunochemotherapy.

None of our patients developed grade 3 or grade 4 hepatotoxicity, and none required discontinuation of R-CHOP owing to hepatotoxicity or other causes. However, the 3 patients (3 of 28 patients) who developed enzyme flare (grade 2) delayed their scheduled therapy but continued again after normalization of liver enzymes with a median time of delay 10 days (range 7–14 days) and that comes in agreement with results of Nishikawa et al. [6], Nosotti et al. [11], and Marignani et al. [12].

In addition, viral reactivation occurred in 28.6% of HCV-positive patients (2/7 patients) in our study which was inconsistent with the results of Boyle and Reid [13] who reported that 66.6% of HCV-positive NHL patients (6/9 patients) developed viral reactivation that could be explained as they did not exclude HIV-positive patients and with Ennishi et al. [14] who reported that an increase of HCV-RNA during immunochemotherapy was observed in 5 out of 6 HCV-positive NHL patients (83.3%); this great variation can be explained by different definitions of viral reactivation.

Interestingly, one of the two patients who developed viral reactivation was shifted to salvage chemotherapy for relapse without any further reactivation while the other one died after 7.8 months of diagnosis when shifted to a salvage therapy due to progression of lymphoma and then developed ascites and hepatic encephalopathy without further HCV load reevaluation.

Our study also reported increased HCV-RNA significantly during R-CHOP ($P = 0.049$) and that comes in concordance with many previous reports [7, 10–12], with no significant relation between viral reactivation and development of enzyme flare ($P = 0.43$) and this comes in agreement with Marignani et al. [12] and Merli et al. [10].

In conclusion, our study results suggested that HCV infection might not influence the clinical course in DLBCL patients who received R-CHOP and also HCV-RNA quantification seems to behave irrespectively of ALT levels and may not be useful for predicting liver toxicity but more studies with larger sample size and longer follow-up are needed.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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This work was done at Department of Medical Oncology, Faculty of Medicine, Zagazig University, Sharkia, Egypt.

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