Hepatitis C Virus Reactivation in Patients with Heamatological Malignancies, Single Egyptian Center Study

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Abstract: In Egypt, hepatitis C is highly endemic (up to 15% of the population are chronic infected), in which hepatitis C virus genotype 4 (HCV-4) is the most common type, where HCV is a risk factor for diffuse large B cell, marginal zone, and follicular lymphomas. Hepatitis flare up was defined as three fold or greater increase in serum ALT level, this flaring up may be attributed to reactivation of viral hepatitis, drug hepatotoxicity and or malignant infiltration. Viral reactivation is a well-recognized complication in patients with chronic HCV infection, who received cytotoxic chemotherapy or immunotherapy for cancer. Hepatitis flare up in patients undergoing chemotherapy may jeopardize chemotherapy schedule or even cause lethal hepatic failure of the patients. **Aim of work:** Our study was aiming to assess the possible causes of hepatitis flare up in patients with hematologic malignancies during chemotherapy, to evaluate the possible impact of chemotherapeutic agents on hepatitis C reactivation and to identify risk factors that may promote viral reactivation in those patients. **Patients and Methods:** This study was carried out in Gasrtroentrology and Hepatology, Hematology and Medical Oncology Units, Internal Medicine Department in collaboration with Clinical Pathology Department, Zagazig University Hospital during period between June 2011 and December 2012. A total of 60 consecutive patients with different types of hematological malignancies,16 patients had NHL, 5 patients had HD, 15 patients had ALL, 5 patients had AML, 10 patients had CML, 4 patients had CLL and 5 patients had MM were included in this study. Based on serum markers testing for HCV, patients were classified into two groups: Group (A): included 29 patients who had HCV infection. Group (B): included 31 patients in whom viral markers tests were negative. All patients were subjected to a complete history and physical examination, routine laboratory investigations including: Complete blood picture, Liver function tests (ALT, AST, S. Albumin, S. Bilirubin and INR), Blood urea and serum creatinine, random blood glucose, E.S.R., L.D.H, Serum Uric acid, viral hepatitis and radiological studies. Complete blood picture, liver function tests (ALT, AST, S. Albumin, S.Bilirubin and INR), blood urea and serum creatinine were reevaluated after every chemotherapy cycle. All patients had HBsAg and HBc Ab negative tests. **Result:** Eight patients had hepatitis flare up in group A four of them were due to HCV reactivation (4/8 patient 50%) and three patients due to hepatotoxicity (3/8 patient 37.5 %) of chemotherapy and only one patient (1/8) about 12.5% due to malignant infiltration. Our study recorded that only 4 patients in group A out of 29 (13.7%) developed HCV reactivation. In group B hepatitis flare up due to hepatotoxicity of chemotherapy (2/4 patients 50 %) and malignant infiltration (2/4 patients 50%). Hepatitis flare up were noticed frequently in NHL patients subjected to CHOP regimen of chemotherapy. **Conclusion:** We concluded that hepatitis C virus reactivation was a well recognized complication in patients with hematological malignancies who received cytotoxic that may result in poor outcome.

[Emad Emam, Emad F. Hamed, Ehab F. Mostafa, Hesham Attia,Ashraf M. ElHefni and Manal M. El Gaerby. **Hepatitis C Virus Reactivation in Patients with Heamatological Malignancies, Single Egyptian Center Study.** *Life Sci J* 2013;10(2):610-615]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 88

Key words: HCV, Hepatitis flare up, Hematologic malignancies & chemotherapy.

1. Introduction

Hepatitis flare up in patients undergoing chemotherapy may jeopardize chemotherapy schedule or cause severe hepatic damage and even lethal hepatic failure of the patients. (1).Reactivation of HBV infection as a result of shifting of balance between the virus and immune status could lead to disastrous outcome of fulminant hepatic failure and death (2). The reported frequency of HBV reactivation in HBs Ag positive patients with different types of hematological malignancies undergoing chemotherapy has ranged widely from (14-72%) (3-4). Rituximab plus steroid-containing regimens may increase the risk of HBV reactivation in HBs Ag positive patients and also in those with occult HBV infection in lymphoma patients (5). In Egypt, hepatitis C is highly endemic (up to 15% of the population), in which hepatitis C virus genotype 4 (HCV-4) is the most common type (6). HCV is a risk factor for diffuse large B cell, marginal zone, and follicular lymphomas in Egypt (7). HCV reactivation seems to be less common than HBV reactivation and is usually associated with a good outcome and low mortality. However, once severe hepatitis develops, as a result of viral reactivation, mortality rates seem to be similar among patients infected with HBV or

HCV. Liver damage owing to viral reactivation frequently leads to modifications or interruptions of chemotherapy, which can negatively affect the patients clinical outcome (**8**).

The aim of the work: Our study aimed to assess hepatitis flare up in patients with hematologic malignancies during chemotherapy, to evaluate the possible impact of chemotherapeutic agents on hepatitis C reactivation and to identify other risk factors that may promote viral reactivation in those patients

2. Patients and Methods

This study was carried out in Gastroenterology and Hepatology, Hematology and Medical Oncology Units, Internal Medicine Department in collaboration with Clinical pathology Department, Zagazig University Hospital during the period between June 2011 and December 2012. A total of 60 consecutive patients with different types of hematologic malignancies,16 patients had NHL (26%), 5 patients had HD(8.3%), 15 patients had ALL(25%), 5 patients had AML (25 %), 10 patients had CML (16.7%), 4 patients had CLL (6.7%) and 5 patients had MM (8.3%) were included in this study. They were 38 males (63.3%) and 22 females (37.7%).their ages ranged from 12-75 y with mean 40.4±16.7 y.

Methods:

All patients were subjected to complete history, physical examination and routine laboratory investigations including complete blood picture, liver function tests (ALT, AST, S. Albumin, S. Bilirubin and INR), blood urea, serum creatinine, random blood glucose. E.S.R., L.D.H, serum Uric acid and HCV Ab by ELISA **(9).** Complete blood picture, liver function tests (ALT, AST, S. Albumin, S. Bilirubin and INR), blood urea and serum creatinine were reevaluated after every chemotherapy cycle. Routine radiological studies including chest x-ray and Pelvi-abdominal C.T,bone marrow aspiration and/or biopsy and Echo-color Doppler were done. Hepatitis flare up was defined as three fold or greater increase in serum ALT level and this flare up attributed to reactivation of viral hepatitis C proved by threefold or more elevation of HCV RNA compared with pre chemotherapy treatment by HCV RNA quantitative PCR in using TaqMan Real time PCR (stepOne Real-time PCR System, Applied Biosystem), performed strictly in accordance with the manufacturer's instructions.

Based on serum markers testing for HCV, patients were classified into two groups: Group (A): included 29 patients who had HCV infection. Group (B): included 31 patients in whom viral markers tests were negative.

Baseline quantitative PCR for HCV RNA were performed for group (A) patients before initiation chemotherapy and repeated when hepatitis flare was diagnosed **(10,11).**

Patients were excluded from the study before initiation of chemotherapy if they were Hepatitis B surface antigen (HBsAg) positive (Prechek bio, Anaheim, CA, 92801, USA) then confirmed by PCR (stepOne Real-time PCR System, Applied Biosystem) after flare up of enzymes (11, 12)

Treatment Regimen:

All patients were treated by chemotherapy according to their hematological malignancies.

(a) Hodgkin Disease (ABVD protocol every 28 days **(13).**

(b)Non Hodgkin Lymphoma (R-CHOP protocol every 21 days, Rituximab 375mg/m2 IV over 5 hours day1,Cyclophosphamide:750mg/m2 IV Day 1,Doxorubicin 25mg/m2 IV day 1 and Vincristine:1.4mg/m2 IV Day1, Prednisolone:100mg PO for 5 days **(14).**

(c) Acute Lymphoblastic Leukemia (BFM protocol including induction, reinduction, consolidation and maintenance therapy **(15).**

(d) Acute myeloid Leukemia (Induction of remission: cytosine arabinoside 100 mg /m2/D IV. For 7 days, Daunorubucin 45 mg/m2 /D for 3 days and High dose cytosine arabinoside for post induction therapy) **(16).**

(e) Chronic myeloid Leukemia (Imitinibe: 400-800mg/D orally **(17).**

(f) Chronic lymphatic leukemia (Standard treatment is Fludarabine/ cyclophosphamide for three days) **(18).**

(g) Multiple myeloma (VAD protocol every 3weeks) **(19).**

All protocols of chemotherapy were approved by our institutional board, ethical committee and well informed consents were obtained.

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.

3. Results

Our results showed a total of 60 consecutive patients with hematological malignancies(32 had NHL (26%), 5 had HD(8.3%),15 had ALL(25%),5 had AML(8.3%),10 had CML (16.7%),4 had CLL (6.7%) and 5 had MM(8.3%). 29 patients have HCV

Ab positive, 31 patients have negative viral markers. They were 31 males (51.7%) and 29 females (48.3%), their ages ranged from 12-75 years with mean 40.4±16.7 y.

Group (A) included 20 males (69%) and 9 females (31%) and their ages ranged from 19-65 years with mean 40.6 ± 19.7 and they had positive test for HCV infection.

Hematological malignancies of this group, 2 patients had HD(6.9%), 6 had NHL(20.7%),7 had ALL (24.1`%), 2 had AML (6.9%), 7 had CML (24.1`%), 3 had CLL (10.3%), and 2 had M.M (6.9%).

In this group eight patients had flare up four of them were due to HCV reactivation (4/8 patients 50%), three patients due to hepatotoxicity (3/8 patient 37.5 %) of chemotherapy and only one patient due to malignant infiltration (1/8 patient12.5%)

Group (B) included 18 males (58.1%) and 13 females (41.9%) and their ages ranged from 15-70 years with mean 39.1 ± 18.6. This entire group was sero negative for HCV markers.

Hematological malignancies of this group were 3 had HD (9.7%),10 had NHL(32.3%),8 had ALL (25.8`%), 3 had AML (32.3%), 3 had CML (32.3`%), 1 had CLL (3.2%), and 3 had M.M (32.3%).

In this group flare up of enzymes due to hepatotoxicity of chemotherapy (2/4 patients 50 %) and two patient due to malignant infiltration.

The eight patients who developed flare up in group (A), their ages ranged from 15-65 years, 6 were males and 2 were females. 4/8 had NHL(50%) received R/ CHOP chemotherapy,one patient had ALL (12.5%) received BFM protocol, one patient had CML(12.5%) received Imitinibe, one patient had AML(12.5%) received 3+7 protocol of Cytosine A.-Daunorubucin Chemotherapy and lastly one patient had Multiple myeloma (12.5%) received VAD protocol of chemotherapy. However there were 21 patients didn´t developed flare up and in this group their ages ranged from 20-65 years. Fourteen patients were males and 7 were females in which 6 had NHL (28.6%) received R/ CHOP chemotherapy,4 patients had ALL (19%), one patient had AML(4.8%), 4 patients had CML(19%), 2 patients had MM(9.5%), 2 patients had CLL(9.5%) and lastly 2 patients had HD(9.5%).

In our result we reported that there were 4 patients developed flare up in group (B) with age range from 18-43 years. Three patients were males and 1 was female in which 2/4 had NHL(50%) received R/CHOP chemotherapy, one patient had ALL (25%) received vincrestine, prednisone and daunorubucin chemotherapy, one patient. had HD (25%) received ABVD chemotherapy however there were 27 patients didn´t developed flare up in this group with age range from 15-75 years, 20 were males and 7 were females in which 4/27 had NHL (14.8%) received R/ CHOP chemotherapy, 9/27 patient had ALL (33.3%) received Vincrestine, prednisone and daunorubucin chemotherapy, 3/27 patients had AML (11.1%) received cytosine arabinoside and daunorubucin chemotherapy, 5 patients had CML (18.5%) received imitinibe Chemotherapy, 2 patients had multiple myeloma (7.41%) received VAD protocol of chemotherapy, 2 patients had CLL (7.41%) received fludrabine/cyclophosphamide chemotherapy and lastly 2 patients had HD(7.41%)received ABVD chemotherapy.

Our study showed that hepatitis flare occur mostly during treatment of NHL (50%) 4/8 patients of group A and 2/4 patients in group B, followed by other hematological malignancies. also showed that hepatitis flare occur mostly during R/CHOP chemotherapy (50%) 4/8 patients of group A have NHL and 2/4 patients of group B have NHL, followed by other chemotherapies.

There were four cases, 3 were males and one was female with age range from 18-50 years developed flare up due to HCV reactivation in group A.

Table 1: Hepatitis flare in group A and B in relation to type of hematological malignancies

	Group (A) n:29		Group (B) n:31		X^2	*P*
NO. flare up	**8**	**27.5%**	**4**	**12.9%**		
Hematological Malignancies:						
Lymphoma						
HD	**0**	**0%**	**1**	**25%**	**0.14**	**0.71**
NHL	**4**	**50%***	**2**	**50%***	**0.0**	**1.0**
Leukemia						
ALL	**1**	**12.5%**	**1**	**25%**	**0.08**	**0.78**
AML	**1**	**12.5%**	**0**	**0 %**	**0.14**	**0.71**
CML	**1**	**12.5%**	**0**	**0 %**	**0.14**	**0.71**
CLL	**0**	**0%**	**0**	**0 %**	**0.0**	**1.0**
MM	**1**	**12.5%**	**0**	**0 %**	**0.14**	**0.71**

Table 2: Hepatitis flare in all patients in relation to type of Chemotherapy

	Group (A)		Group (B)		X^2	*P*
	Number (8)	%	Number(4)	%		
Chemotherapy:						
ABVD	**0**	**0%**	**1**	**25%**	**0.14**	**0.71**
CHOP	**4**	**50%***	**2**	**50%***	**0.0**	**1.0**
BMF 89 protocol	**1**	**12.5%**	**0**	**0%**	**0.0**	**1.0**
Imatinib 3 and 7 protocol	**1**	**12.5%**	**1**	**25 %**	**0.08**	**0.78**
VAD protocol	**1**	**12.5%**	**0**	**0%**	**0.14**	**0.71**
Fludrabine& Cyclophosphamide	**1**	**12.5%**	**0**	**0 %**	**0.14**	**0.71**
	0	**0 %**	**0**	**0 %**	**0.0**	**1.0**

Table 3: Clinical details &outcome of patients with hepatitis flare up in group A

	Case 1	Case2	Case 3	Case4	Case5	Case6	Case7	Case8
Age	**33 y**	**15 y**	**35 y**	**15 y**	20	33	48	30
Sex	**female**	**male**	**female**	**male**	**male**	**male**	**male**	**Male**
Type of malign.	**NHL**	**NHL**	**NHL**	**NHL**	ALL	CML	AML	MM
Chemotherapy Regimen	**R/CHOP**	**R/CHOP**	**R/CHOP**	**R/CHOP**	BFM	Imitinibe	Cytosine A.-Daunorubicin	VAD
No. of cycles prior to reactivation	**3**	**4**	**4**	**2**	3	2	3	2
Base-line HCV Load (IU/CC)	**90000**	**3000**	**4000**	**80000**	50000	4000	5500	50000
viral reactivation, HCV Load (IU/CC)	**1,100,0000**	**1,700,0000**	**1,800,0000**	**1,005,0000**	-----	-------	------	------
Outcome of viral reactivation	**STOP CHEMOTHERAPY**	**LOST**	**LOST**	**STOP CHEMOTHERAPY**	**STOP CHEMOTHERAPY**	**STOP CHEMOTHERAPY**	**STOP CHEMOTHERAPY**	**STOP CHEMOTHERAPY**

Table 4: Clinical details &outcome of patients in group (B) who develop hepatitis flare

	Case 1	Case2	Case 3	Case 4
Age	**15 y**	**30 y**	**38 y**	**43 y**
Sex	**male**	**male**	**female**	**male**
Type of malign.	**NHL**	**HD**	**ALL**	**NHL**
Chemotherapy Regimen	**R/CHOP**	**ABVD**	**BMF 89**	**R/CHOP**
No. of cycles prior to reactivation	**4**	**3**	**2**	**5**
Causes of hepatitis flare	**Hepatotoxicity of chemotherapy**	**Infilteration**	**Hepatotoxicity of chemotherapy**	**Infiltration**
Outcome of viral reactivation	**STOP CHEMOTHERAPY**	**STOP CHEMOTHERAPY**	**STOP CHEMOTHERAPY**	**Lost**

4. Discussion

Hepatitis C was not only a hepatotropic but also a lymphotropic agent as a consequence of the lymphatic infection, several lymphoproliferative disorders (LPDs) have been associated with this virus including mixed cryoglobulinemia (MC), B-cell non-Hodgkin's lymphoma (NHL) and monoclonal gammopathies.Several hypotheses, frequently interconnected with each other, had been proposed in regard to the possible mechanisms of HCV-related lymphomagenesis and these included a key role played by the sustained antigenic stimulation of the B-cell compartment, the role of viral lymphotropism and viral proteins, chromosomal aberrations, cytokines, and microRNAs **(20).**

Infections with hepatitis C virus (HCV) are associated with significant morbidity and mortality among patients with cancer, especially in patients with hematologic malignancies and those who undergo chemotherapy **(21).** Hepatitis flares may become a more common problem in cancer patients during cytotoxic treatment.

Zuckerman recorded hepatitis C reactivation in 8 patients (23.5%), malignant hepatic infiltration in 2 patients (6%), and the use of hepatotoxic chemotherapeutic agents in 7 patients (20.6%). The causes of hepatitis were unknown in 2 patients (5.9 %). **(22).**

Our results recorded out of 60 consecutive patients with hematological malignancies were included, 12 patients (20%) developed hepatitis flare up, HCV reactivation 4 cases (6.7%), 5 cases hepatotoxicity (8.3%) and 3 cases with malignant infiltration (5%).

Our study showed only 4 HCV patients out of 29 (13%) developed reactivation proved by elevated enzymes and increase of viral load. Hepatitis C virus (HCV) infection generally leaded to chronic hepatitis and was one of the leading causes of hepatocellular carcinoma and liver transplantation worldwide.However, little was known about acute exacerbation and reactivation of chronic HCV infection in patients with cancer. Most of the reported cases of liver dysfunction in HCV-infected cancer patients occur in those with hematological malignancies, mainly non-Hodgkin lymphomas **(23).**

These results were in agreement with our study in which hepatitis flare up is more frequent in patients with NHL 6 patients out of 12 in comparison to other hematological malignancies.

HCV-positive status may represent a risk factor for the development of hepatic flares in B-cell NHL patients receiving rituximab-containing regimens equal 11% **(22)** and this was in agreement with our study in which 6 HCV patients out of 29 (20.6%) developed reactivation.

Hepatitis flares may result in a delay or failure to complete chemotherapy and in a prospective study of patients with NHL treated with CHOP chemotherapy, premature cessation or delay in chemotherapy occurred in 71% of patients with HCV and HBV reactivation compared to 33% of patients without evidence of reactivation. **(24)**. In our study 2 patients out of 4 who developed HCV reactivation (50%) stop chemotherapy, 1 patients (25%) were lost and only one patient continue CHOP without predinsolone (25%).

Recommendation

Close monitoring and putting of consideration flare up in patients with hematologic malignancies during chemotherapy, to evaluate the possible impact of chemotherapeutic agents on hepatitis C reactivation and to identify other risk factors that may promote viral reactivation in those patients.

Conclusion

Hepatitis C virus reactivation was a well described complication in patients with hematological malignancies who received cytotoxic chemotherapy and might result in varying degrees of liver damage.

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3/16/2013