OPEN ACCESS Freely available online

Journal of Hepatology and Gastrointestinal Disorders

Research Article

Hepatitis C and its Outcome in Patients of Malignancy Receiving Chemotherapy in Comparison to Non-Malignant Patients

Dawood Banday[1], Ashaq Hussain Parrey[2*], Bilal Rather[1]

[1]Department of Internal Medicine, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India;[2]Department of Internal Medicine, Government Medical College and Associated Hospital, Srinagar, Jammu and Kashmir, India

ABSTRACT

Introduction: Hepatitis C virus (HCV) is an RNA virus that belongs to the family of flaviviruses. Chronic hepatitis C infection is a very common disease globally affecting over 180 million people. It is a leading cause of chronic hepatitis, cirrhosis, and liver cancer and a primary indication for liver transplantation. As we move to the new era of oral antivirals as the treatment of hepatitis C we needed to see their efficacy and safety in patients with hepatitis C and underlying malignancy compared to the patients with hepatitis C without malignancy. Patients with malignancy with hepatitis C respond equally to the treatment of hepatitis C as patients without malignancy.

Aims and objectives: The aim of the study was to find the outcome of treatment in patients with Hepatitis C with malignancy receiving Chemotherapy in Comparison to non-malignant patients with hepatitis C with oral *versus* parenteral antiviral.

Results: Out of 80 patients 38 patients which were confirmed HCV positive had malignancy and were on chemotherapy protocol were studied and compared with 42 patients of HCV positive without any malignancies. Initial response to treatment in malignant cohort was blunted (60.5% malignant patients with high viral load ($p=<0.001$) after 12 weeks), which later improved over treatment duration. Treatment complications were more common in malignant cohort as expected. Response was equivalent in IFN α *versus* Protease inhibitor sofosbuvir group.

Conclusion: Patients with malignancy on chemotherapy fared not inferior to patients without malignancies on HCV treatment.

Keywords: Hepatitis C; Malignancy; Oral antivirals; Parenteral; Outcome

INTRODUCTION

Hepatitis C Virus (HCV) is a RNA virus that belongs to the family of flaviviruses. It is a linear, single stranded, positive sense 9600-nucleotide RNA virus. HCV is the only member of the genus Hepacivirus in the family Flaviviridae. The HCV virion is an enveloped virus 50 nano microns in diameter. The two enveloped proteins, E1 and E2, heterodimers and assemble into tetramers, which create smooth outer layer. This layer has a "fishbone" configuration with icosahedral symmetry. The envelope proteins are anchored to a host cell-derived lipid bilayer envelope membrane that surrounds the nucleocapsid. The nucleocapsid is believed to be composed of multiple copies of the core proteins and forms an internal icosahedral viral coat that encapsulates the genomic Ribonucleic acid (RNA). HCV circulates in various forms in the serum of an infected host, including virions that are bound to very-low-density and low-density lipoproteins and appear to represent the infectious fraction virions bound to immunoglobulins and free virions.

Although peripheral blood mononuclear cells, B cells, T cells, and dendritic cells have been reported to support HCV replication, hepatocytes are the major site of viral replication. Early viral binding to the hepatocyte surface is still not completely understood. HCV entry involves the attachment of envelope proteins E1 and E2 to cell surface molecules. Once the HCV virus attaches to the cell, endocytosis of the bound virion is presumed to occur, as in other flaviviruses and release of viral RNA into the cytoplasm. In the cytosol the HCV RNA docks to a site on the endoplasmic reticulum and mediates cap-independent internal initiation of HCV polyprotein translation. The large polyprotein generated by translation of the HCV genome is co- and post-translationally

Correspondence to: Ashaq Hussain Parrey, Department of Internal Medicine, Government Medical College and Associated Hospital, Srinagar, Jammu and Kashmir, India, E-mail: chogalpora@gmail.com

Received: 17-Mar-2022, Manuscript No. JHGD-22-16393; **Editor assigned:** 21-Mar-2022, PreQC No. JHGD-22-16393 (PQ); **Reviewed:** 05-Apr-2022, QC No. JHGD-22-16393; **Revised:** 09-Apr-2022, Manuscript No. JHGD-22-16393 (R); **Published:** 16-Apr-2022, DOI:10.35248/2475-3181.8.22.202.

Citation: Parrey AH, Banday D, Rather B (2022) Hepatitis C and its Outcome in Patients of Malignancy Receiving Chemotherapy in Comparison to Non-Malignant Patients. J Hepatol Gastroint Dis. 8:202.

processed proteolytically into at least 11 viral proteins, including both structural (nucleocapsid [C], or Glycoprotein (GP) 21; envelope1 [E1], or GP 31; and envelope2 [E2], or GP 70) and nonstructural (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) proteins. Finally, viral particle formation is initiated by the interaction of the core protein with genomic RNA in the endoplasmic reticulum, although the details of this process and subsequent export of mature virions from the hepatocyte are poorly understood.

Multiple studies in high prevalence areas of Hepatitis C Virus (HCV) infection have shown that the frequency of HCV infection was higher in patients with B-cell lymphoma, particularly those with low grade marginal-zone lymphoma and primary hepatosplenic B-cell lymphoma. Increased prevalence of HCV infection has been reported among patients with Diffuse Large-Cell Lymphoma (DLCL). Treatment and outcome of patients with DLCL and HCV infection are still a matter for debate. Particularly, the liver toxicity of aggressive and/or intensive chemotherapies in patients with HCV infection is not well known.

As we move to the new era of oral antivirals as the treatment of hepatitis C we needed to see their efficacy and safety in patients with hepatitis C and underlying malignancy compared to the patients with hepatitis C without malignancy.

Aims and objectives

The aim of the study was to find the outcome of treatment in patients of hepatitis C with malignancy receiving chemotherapy in comparison to non-malignant patients with hepatitis C with oral *versus* parenteral antiviral drugs.

MATERIALS AND METHODS

Study design

The present study is a single-center observational, retrospective as well as prospective study.

Patient population

The present study was conducted in the department of Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences, Kashmir between September 2013 and March 2015. All patients with RT-PCR documented hepatitis C virus infection were considered for this study.

Inclusion criteria

Patients was considered eligible for inclusion if

1. Patients who have any histopathologically documented malignancy on active chemotherapy with documented HCV infection.

2. Patients with documented HCV infected patients without any malignancy.

Exclusion criteria

1. Concomitant Liver disease of other etiology.

2. Pregnancy.

RESULTS

During the study period of 2 years, 80 HCV positive patients were enrolled in our study. The mean age of the patients was 38.3 years with range of 5 years to 81 years. From the 80 patients, 38(47.5%) were having some malignancy denoted as Group A and 42(53.5%) were not having any malignancy denoted as Group B. Mean Age in Group A was 39.29 years with a range of 5-74 years while mean age in Group B was 37.36 years with a range of 7-81 years. There was no statistically significant difference between the two groups in terms of Age (p=0.667). HCV genotype was predominantly of 2(28.9%) and 3(47.4%) type (Table 1).

In Group A, 21patients (55.3%) were males and 17 patients (44.7%) were females (ratio=1.3:1), while in Group B, 23 patients (54.8%) were males and 19 patients (45.2%) were females (ratio=1.2:1). When compared with respect to gender, there was no statistically significant difference between the two groups (p=0.964). In terms of genotypes, Type 2 (38.1%) and Type 3 (47.6%) were common among males, while Type1 (23.5%) and Type 3 (47.1%) were common among females.

In Group A, 32(84.2%) had no history of blood transfusion or blood products, while in Group B, 38(90.5%) had no such history. There was no statistically significant difference between the two groups in terms of history of blood transfusions (p=0.612). Smoking history was present in 15(39.5%) in Group A while in Group B, it was 14(33.3%) showing no significant statistical difference (p=0.682).

Pursuing history of environmental exposure, Dental extraction history was present in 20(52.6%) in Group A *versus* 24(57.1%) in Group B with no statistically significant difference. Likewise, needle prick history was present in 3(7.9%) in Group A *versus* 4(9.5%) in Group B. Similarly, razor sharing history was present in 2(5.3%) in Group A *versus* 5(11.9%) in Group B having no statistical significant difference. Sharing needles for injection was present in 1(2.6%) in Group A *versus* 2(4.8%) in Group B with no statistical significant difference. There was 1(2.6%) patient in Group A with history of I/V drug abuse, and none from Group B. Alcohol abuse was present in 6(15.7%) patients from Group A and 1(2.4%) from Group B. Promiscuous sexual activity was present in 1(2.6%) from Group A and none from Group B. History of past surgery was present in 20(52.6%) in Group A and 26(61.9%) in Group B with no significant statistical difference (Table 2).

Table 1: HCV genotype in different age group of studied population.

Age of patient in years	HCV genotype				Total
	1	2	3	4	
<20	0	4	6	0	10
20-39	1	2	4	0	7
40-59	3	4	5	2	14
>60	2	1	3	1	7
Total	6	11	18	3	38

Table 2: Showing risk factors for hepatitis infection in studied population.

Parameters	Values	
	Group A	Group B
Total cases	38	42
Smoking	15(39.5%)	14(33.3%)
Dental extraction	20(52.6%)	24(57.1%)
Needle prick	3(7.9%)	4(9.5%)
Sharing razor	-5.30%	5(11.9%)
Sharing needles for injections	1(2.6%)	2(4.8%)
Blood and blood products	6(15.8%)	4(9.5%)
I/V drug abuse	1(2.6%)	0
Alcohol abuse	6(15.7%)	1(2.4%)
Promiscuous sexual Activity	1(2.6%)	0

Group A contains HCV positive patients with malignancies. Solid malignancies were 19(50.0%) and haematological malignancies were 19(50.0%). Among solid malignancies, genotype 3(10, 52.6%) was most common and among haematological malignancies, genotype 2(9, 47.4%) was commonest closely followed by Type 3 (8 , 42.1%).

HCV genotype in our study

As we know, HCV has 4 different genotypes with varying geographical pattern and therapeutic response. In our study, most common genotype seen were Type3 (32, 40.0%) followed by Type 2 (25, 31.3%) then Type1 (15, 18.7%) and lastly Type 4 (8, 10.0%). In Group A, Type 3 was most common (18, 47.4%) followed by Type 2 (11, 28.9%) then Type 1 (6, 15.8%) and Type 4 (3, 7.9%). Similarly, in Group B, Type 3 was most common (14, 33.3%) equaling Type 2 (14, 33.3%) followed by Type 1 (9,21.4%) and Type 4 (5, 11.9%).There was no significant statistical difference observed between the two groups (p=0.623) Table 3.

Treatment

Patients received two different regimens in vogue for HCV treatment, IFN-α based regimen and protease inhibitor sofosbuvir based regimen. Overall, 52(65.0%) received IFN-α based regimen and 28(35.0%) received sofosbuvir based regimen. Among all groups, Group A received IFN-α based regimen in 22(57.9%) cases while sofosbuvir in 16(42.1%) patients .Similarly, Group B received IFN- in 30(71.4%) patients while 12(28.6%) patients were put on sofosbuvir based regimen. No significant statistical difference was noted (p=0.205) (Table 4).

Response

Liver enzymes were measured at baseline before starting treatment, at 12weeks of treatment and at end of treatment as measurement of severity of disease.

Alaninetransaminase (ALT) was graded as normal (≤ 40IU/L), mild increase (41-100IU/L), moderate increase (101-400IU/L) and severe increase (>400IU/L).

At baseline, in Group A, 23.7% patients had severe increased levels of ALT as compared to Group B (45.2%) while as Group A had 50.0% patients with Moderate increase in ALT levels as compared to Group B (54.8%). However Group B had no patient in normal or mild category which is statistically significant (p=0.003).

At 12 weeks of treatment, trend stabilized with no statistical significant difference observed in ALT levels (p=0.314).

At end of treatment, 95.2% of Group B patients had ALT normalized as compared to 76.3% observed in Group A with most of them settling at mild increased level (21.1%). This difference was statistically significant (p=.046) (Table 5). Also, bilirubin levels were measured as a marker of liver injury. It was also categorized into normal (≤ 1.5 mg/dl), mild increase (1.6-3.0 mg/dl), moderate increase (3.1-6.0 mg/dl) and severe increase (>6.0 mg/dl).

At baseline, Group B had 66.7% patients with moderate increase in bilirubin levels as compared to Group A (39.5%) which was statistically significant (p=0.018).

At 12 weeks, 42.9% of the patients of Group B were in normal category while as rest were equally distributed between mild and moderate category. While as, in Group A, very less patients (7.9%) were retained in moderate category. This difference was statistically significant (p=0.048).

At end of treatment, most patients had normalized Bilirubin levels, 81.6% in Group A and 92.9% in Group B (p=0.236) (Table 6). Similarly, severity of infection was measured by HCV RNA load. It was divided into not detected (0 copies/ml), low (1-1000 copies/ml), high (1001-100000 copies/ml) and very high load (>100000 copies/ml).

At baseline, 81.6% of Group A patients were having very high load while as only 40.5% Group B patients belonged to this category. Moreover, good number of Group B patients (52.4%) belonged to high load category against only18.4% from Group A (p=0.001).

At 12 weeks, remarkable 85.7% Group B patients responded and load dropped to low not detected level as against only 18.4% from Group A and 60.5% of Group A patients were in high load category (p=<0.001).

At end of treatment, in both Groups, all patients attained remission with no detectable level of viral copies (Table 7).

Complications

Anemia was graded as none (>12 g/dl), mild (10.0-11.9 g/dl), moderate (7.0-9.9 g/dl) and severe (<7.0 g/dl). Lowest recorded Hb level during whole treatment period was considered.

In Group A, 94.7% developed Anemia mostly in moderate category (452.1%) while as Group B had mild-no anemia in 90.5% of patients (p=<0.001). This effect may be due to concomitant chemotherapy in Group A patients. 10 patients of Group A needed with holding chemotherapy till their Hb level improved against only 2 in Group B.

Similarly, leukopenia was seen in 52.6% patients of Group A with severe leucopenia in 18.4%. As against it, only 4.8% patients from Group B had leucopenia (p=<0.001). 7 patients required with holding chemotherapy.

Thrombocytopenia (<100,000 platelets/mm^3) was observed in 84.2% patients in Group A as compared to 85.7% in Group B. Severe to critical thrombocytopenia occurred in 1 patient in Group A compared to 10 patients in Group B (p=0.105). However, only 1 patient developed epistaxis (Table 8).

Table 3: Distribution of HCV genotype in two groups.

Genotype	Group A [n=38]		Group B [n=42]		P-value
	Number	Percentage (%)	Number	Percentage (%)	
1	6	15.8	9	21.4	0.623
2	11	28.9	14	33.3	
3	18	47.4	14	33.3	
4	3	7.9	5	11.9	

Table 4: Significant statistical difference.

HCV Type	Group A		Group B		P-value
	Number	Percentage (%)	Number	Percentage (%)	
IFN/Ribavarin	22	57.9	30	71.4	0.205
Sofosbuvir	16	42.1	12	28.6	
Total	38	100	42	100	

Table 5: In ALT levels, no statistical significant difference is observed.

ALT (IU/L)		Group A [n=38]		Group B [n=42]		P-value
		Number	Percentage (%)	Number	Percentage (%)	
Baseline	≤ 40	1	2.6	0	0	0.003
	41-100	9	23.7	0	0	
	101-400	19	50	23	54.8	
	>400	9	23.7	19	45.2	
12 Week	≤ 40	8	21.1	5	11.9	0.314
	41-100	24	63.2	33	78.6	
	101-400	6	15.8	4	9.5	
	>400	0	0	0	0	

Table 6: Statistical representation of normalized Bilirubin level in patients.

Bilrubin (mg/dl)		Group A [n=38]		Group B [n=42]		P-value
		Number	Percentage (%)	Number	Percentage (%)	
Baseline	≤ 1.5	6	15.8	0	0	0.018
	1.6-3.0	9	23.7	7	16.7	
	3.1-6.0	15	39.5	28	66.7	
	>6.0	8	21.1	7	16.7	
12 Week	≤ 1.5	18	47.4	18	42.9	0.048
	1.6-3.0	17	44.7	12	28.6	
	3.1-6.0	3	7.9	12	28.6	
	>6.0	0	0	0	0	
End	≤ 1.5	31	81.6	39	92.9	0.236
	1.6-3.0	7	18.4	3	7.1	
	3.1-6.0	0	0	0	0	
	>6.0	0	0	0	0	

Table 7: Patients attained remission with no detectable level of viral copies.

HCV Load (copies/ml)		Group A [n=38]		Group B [n=42]		P-value
		Number	Percentage (%)	Number	Percentage (%)	
Baseline	0-1000	0	0	3	7.1	0.001
	10001-100000	7	18.4	22	52.4	
	>100000	31	81.6	17	40.5	
12 Week	0-1000	7	18.4	36	85.7	<0.001
	10001-100000	23	60.5	6	14.3	
	>100000	8	21.1	0	0	
End	0-1000	38	100	42	100	-
	10001-100000	0	0	0	0	
	>100000	0	0	0	0	

Table 8: Comparison based on withholding anti-HCV treatment in two groups.

	Group A [n=38]		Group B [n=42]		P-value
	Number	Percentage (%)	Number	Percentage (%)	
IFN/Ribavarin	12	31.57	7	16.67	0.009
Sofosbuvir	6	15.78	2	4.76	
Not withheld	20	52.63	33	78.57	

DISCUSSION

Present study was conceived to probe clinical and biochemical profile and genotype presence in Kashmir of HCV patients who have been diagnosed with a malignancy on active anti-cancer chemotherapy. And compare the same with those with HCV positive individuals with no malignancy.

Before delving in to the subject, we have no base line study to compare with. Some authors have studied HCV patients having only NHL (B cell NHL), others have studied post bone-marrow transplant patients with HCV (HCV bonemarrow transplant), and few have studied HCV patients with hematological malignancies. All the studies were done when oral anti-HCV therapy wasn't available. Now, with the introduction of oral direct antiviral agents, these drugs needed to be studied and compared with purely IFN/Ribavarin based regimens and inter-cohort comparison of malignancy patients on active cancer chemotherapy patients and non-malignancy patients.

Chronic hepatitis C infection is a very common disease globally affecting over 180 million people. It is a leading cause of chronic hepatitis, cirrhosis, and liver cancer and a primary indication for liver transplantation.

Due to non-availability of other oral antivirals apart from sofosbuvir in Kashmir, Standard of Care (SOC) was PEGylated interferon based regimen for genotype 2 and genotype 3 for 24 weeks and additional sofosbuvir based regimen for genotype 1 and genotype 4 for 24 weeks.

Numerous studies in high prevalence area of Hepatitis C Virus (HCV) infection have shown that the frequency of HCV infection was higher in patients with B-cell lymphoma, particularly those with low grade marginal-zone lymphoma and primary hepatosplenic B-cell lymphoma [1-8]. Studies by Besson et al. have also shown an increased prevalence of HCV infection among patients with Diffuse Large-Cell Lymphoma (DLCL) [9,10]. Treatment and outcome of patients with DLCL and HCV infection are still a matter for debate. Particularly, the liver toxicity of aggressive and/or intensive chemotherapies in patients with HCV infection is not well known [1]. In Brazil, the hepatitis C test only became mandatory for blood donors in 1993 [11]. The prevalence of HCV infection in patients who had BMT before screening varies from 4.8 to 70% [12]. The virus infection may change the natural history of those patients, in the short term, increasing the risk of serious Venocclusive Disease (VOD) of the liver and susceptibility to GVHD. With recovery of cellular immunity after transplantation, severe hepatitis and fulminant liver failure may occur [13]. In the long term, affected patients may develop an accelerated course of chronic liver disease leading to cirrhosis and to Hepatocellular Carcinoma (HCC) more rapidly than virus carriers who have not had a BMT [14]. Projections about these risks have been based on case reports and studies of patients by Ivantes et al. with a survival rate of about 10 years, some of them significantly differing in regard to the importance of the HCV in the post-BMT [15-18]. Today, with a worldwide BMT history of more than 30 years, hepatitis C in long term survivors requires special attention [19].

Several studies have shown that the frequency of Hepatitis C Virus (HCV) infection is high in patients with B-cell Non-Hodgkin's Lymphoma (NHL). In these studies, liver dysfunction during chemotherapy has been demonstrated, but changes in HCV Ribonucleic acid (RNA) levels during chemotherapy have not been well documented. In this study by Ennishi et al. they monitored serum HCV RNA levels and liver function in five HCV-infected patients with B-cell NHL undergoing treatment with rituximab-combination chemotherapy. Increased HCV RNA levels during or after the chemotherapy was observed in all five patients and a significant increase in transaminases was seen in one case. In this case, serum HCV RNA level dramatically decreased at the time of the increase of transaminases, and this suggested that the cause of liver damage was an immune reaction against hepatocytes with HCV and not any anticancer drug induced liver toxicity. Monitoring of serum HCV RNA levels and transaminases may be helpful to understand the cause of liver dysfunction in patients receiving chemotherapy. However, increases of HCV viral load were not associated with the occurrence of liver dysfunction in this study. Several studies have reported treatment for B-cell Non-Hodgkin's Lymphoma (NHL) in Hepatitis C Virus (HCV)-positive patients; there have also been reports of liver dysfunction related to chemotherapy and Stem Cell Transplantation (SCT) [20-25]. However, changes in HCV load during chemotherapy have not been well studied, and the status of HCV during chemotherapy

is unknown. On the other hand, reactivation in Hepatitis B Virus (HBV)-positive patients during or after chemotherapy is a well-known complication [26,27]. Some authors have recommended monitoring HBV Deoxyribonucleic acid (DNA) level during treatment, because knowing the status of the virus would be helpful l in assessing the risk of reactivation and making decisions about the use of anti-HBV drugs [28-30]. Recently rituximab, a chimeric Mouse/Human Monoclonal Antibody, has become widely used for treatment of CD20-positive B-cell NHL, and there have been reports of reactivation in HBV-positive patients [31,32]. However, reactivation of HCV virus during rituximab treatment has not been reported, and the influence of rituximab against HCV viral load is not well understood [33,34].

CONCLUSION

38 patients of malignancy on chemotherapy protocol which were confirmed HCV positive were studied and compared with 42 patients of HCV positive without any malignancies.

• Most are between 20-40 years of age.

• Genotype 2 and 3 are more common across all age groups and malignancy types.

• Blood transfusion history was more common in malignancy patients although not significantly higher than non-malignant patients.

• Markers of liver injury (ALT, BIL) consistently improved over a treatment period in all genotypes.

• However, there was significantly higher (p=0.003) liver injury in non-malignant patients which improved and fared as in malignant patients over a treatment duration.

• HCV load was higher in genotype 3 *versus* others which improved with standard regimens.

• However, initial response in malignant cohort was blunted (60.5% malignant patients with high viral load (p=<0.001) after 12 weeks), which later improved over treatment duration.

• Patients with malignancy on chemotherapy fared not inferior to patients without malignancies on HCV treatment.

• Treatment complications were more common in malignant cohort as expected.

• Many patients needed with holding HCV treatment (33.8%) for some time (average 2 weeks).

• Response was equivalent in IFN α *versus* Protease inhibitor sofosbuvir group.

REFERENCES

1. Besson C, Canioni D, Lepage E, Pol S, Morel P, Lederlin P, et al. Characteristics and outcome of diffuse large B-Cell lymphoma in hepatitis c virus-positive patients in LNH 93 and LNH 98 groupe d'Etude des lymphomes de l'Adulte programs. J Clin Oncol. 2006;24(6):953-960.

2. Zuckerman E, Zuckerman T, Levine AM, Douer D, Gutekunst K, Mizokami M, et al. Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. Ann Intern Med. 1997;127(6):423-428.

3. Silvestri F, Pipan C, Barillari G, Zaja F, Fanin R, Infanti L, et al. Prevalence of hepatitis C virus infection in patients with lymphoproliferative disorders. Blood. 1996;87 (10):4296-4301.

4. Ferri C, Caracciolo F, Zignego AL, Civita LL, Monti M, Longombardo G, et al. Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. Br J Haematol. 1994;88(2):392-394.

5. Guida M, D'Elia G, Benvestito S, Casamassima A, Micelli G, Quaranta M, et al. Hepatitis C virus infection in patients with B-cell lymphoproliferative disorders. Leukemia. 2002;16(10):2162-2163.

6. De Rosa G, Gobbo ML, De Renzo A, Notaro R, Garofalo S, Grimaldi M, et al. High prevalence of hepatitis C virus infection in patients with B-cell lymphoproliferative disorders in Italy. Am J Hematol. 1997;55(2):77-82.

7. Mazzaro C, Zagonel V, Monfardini S, Tulissi P, Pussini E, Fanni M, et al. Hepatitis C virus and non-Hodgkin's lymphomas. Br J Haematol. 1996;94(3):544-550.

8. Mele A, Pulsoni A, Bianco E, Musto P, Szklo A, Sanpaolo MG, et al. Hepatitis C virus and B-cell non-Hodgkin lymphomas: An Italian multicenter case-control study. Blood. 2003;102(3):996-999.

9. Vallisa D, Bertè R, Rocca A, Civardi G, Giangregorio F, Ferrari B, et al. Association between hepatitis C virus and non-Hodgkin's lymphoma, and effects of viral infection on histologic subtype and clinical course. Am J Med. 1999;106(5):556-560.

10. Luppi M, Longo G, Ferrari MG, Ferrara L, Marasca R, Barozzi P, et al. Additional neoplasms and HCV infection in low-grade lymphoma of MALT type. Br J Haematol. 1996;94(2):373-375.

11. De Vita S, Sacco C, Sansonno D, Gloghini A, Dammacco F, Crovatto M, et al. Characterization of overt B-cell lymphomas in patients with hepatitis C virus infection. Blood, J Am Society Hematol. 1997;90(2):776-782.

12. Ivantes CA, Amarante H, Ioshii SO, Pasquini R. Hepatitis C virus in long-term bone marrow transplant survivors. Bone Marrow Transplant. 2004;33(12):1181-1185.

13. Strasser SI, McDonald GB. Gastrointestinal and hepatic complications. Thomas' hematopoietic cell transplantation. 2003:769-810.

14. Strasser SI, Myerson D, Spurgeon CL, Sullivan KM, Storer B, Schoch HG, et al. Hepatitis C virus infection and bone marrow transplantation: A cohort study with 10-year follow-up. Hepatology. 1999;29(6):1893-1899.

15. Locasciulli A, Bacigalupo A, VanLint MT, Cavalletto D, Pontisso P, Testa M, et al. Hepatitis C virus infection and liver failure in patients undergoing allogeneic bone marrow transplantation. Bone Marrow Transplant. 1995;16(3):407-411. [Google Scholar]

16. Ljungman P, Johansson N, Aschan J, Glaumann H, Lonnqvist B, Ringden O, et al. Long-term effects of hepatitis C virus infection in allogeneic bone marrow transplant recipients. Blood. 1995;86(4):1614–1618.

17. Akiyama H, Yoshinaga H, Tanaka T, Hiruma K, Tanikawa S, Sakamaki H, et al. Effects of cyclosporin A on hepatitis C virus infection in bone marrow transplant patients. Bone Marrow Transplant. 1997;20(11):993-995.

18. Locasciulli A, Testa M, Pontisso P, Bacigalupo A, Ljungman P, Frickhofen N, et al. Hepatitis C virus genotypes and liver disease in patients undergoing allogeneic bone marrow transplantation. Bone Marrow Transplant. 1997;19(3):237-240.

19. Besson C, Canioni D, Lepage E, Pol S, Morel P, Lederlin P, et al. Characteristics and outcome of diffuse large B-Cell lymphoma in hepatitis C virus-positive patients in LNH 93 and LNH 98 groupe d'Etude des lymphomes de l'Adulte programs. J Clin Oncol. 2006;24(6):953-960.

20. Kanamori H, Fukawa H, Maruta A, Harano H, Kodama F, Matsuzaki M, et al. Case report: Fulminant hepatitis C viral infection after allogeneic bone marrow transplantation. Am J Med Sci. 1992;303(2):109-111.

21. Zuckerman E, Zuckerman T, Douer D, Qian D, Levine AM. Liver dysfunction in patients infected with hepatitis C virus undergoing chemotherapy for hematologic malignancies. Cancer. 1998;83(6):1224-1230.

22. Luppi M, Longo G, Ferrari MG, Ferrara L, Marasca R, Barozzi P, et al. Additional neoplasms and HCV infection in low-grade lymphoma of MALT type. Br J Haematol. 1996;94(2):373-375.

23. Kawatani T, Suou T, Tajima F, Ishiga K, Omura H, Endo A, et al. Incidence of hepatitis virus infection and severe liver dysfunction in patients receiving chemotherapy for hematologic malignancies. Eur J Haematol. 2001;67(1):45-50.

24. Coiffier B. Hepatitis B virus reactivation in patients receiving chemotherapy for cancer treatment: Role of Lamivudine prophylaxis. Cancer Investig. 2006;24(5):548-552.

25. Dai MS, Lu JJ, Chen YC, Perng CL, Chao TY. Reactivation of precore mutant Hepatitis B virus in chemotherapy-treated patients. Cancer. 2001;92(11):2927-2932.

26. Hamaki T, Kami M, Kusumi E, Ueyama JI, Miyakoshi S, Morinaga SI, et al. Prophylaxis of hepatitis B reactivation using lamivudine in a patient receiving rituximab. Am J Hematol. 2001;68(4):292-294.

27. Dai MS, Chao TY, Kao WY, Shyu RY, Liu TM. Delayed hepatitis B virus reactivation after cessation of preemptive lamivudine in lymphoma patients treated with rituximab plus CHOP. Ann Hematol. 2004;83(12):769-774.

28. Tsutsumi Y, Kanamori H, Mori A, Tanaka J, Asaka M, Imamura M, et al. Reactivation of hepatitis B virus with rituximab. Expert Opin Drug Saf. 2005;4(3):599-608.

29. Coiffier B, Haioun C, Ketterer N, Engert AA, Tilly H, Ma D, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: A multicenter phase II study. Blood, J Am Society Hematol. 1998;92(6):1927-1932.

30. Vose JM, Link BK, Grossbard ML, Czuczman M, Grillo-Lopez A, Gilman P, et al. Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2001;19(2):389-397.

31. Sarrecchia C, Cappelli A, Aiello P. HBV reactivation with fatal fulminating hepatitis during rituximab treatment in a subject negative for HBsAg and positive for HBsAb and HBcAb. J Infect Chemother. 2005;11(4):189-191.

32. Tsutsumi Y, Kanamori H, Minami H, Musashi M, Fukushima A, Ehira N, et al. Successful treatment of lymphoma with fludarabine combined with rituximab after immune thrombocytopenia induced by fludarabine. Ann Hematol. 2005;84(4):269-271.

33. Arcaini L, Merli M, Passamonti F, Bruno R, Brusamolino E, Sacchi P, et al. Impact of treatment-related liver toxicity on the outcome of HCV-positive non-Hodgkin's lymphomas. Am J Hematol. 2010;85(1):46-50.

34. Ennishi D, Terui Y, Yokoyama M, Mishima Y, Takahashi S, Takeuchi K, et al. Monitoring serum hepatitis C virus (HCV) RNA in patients with HCV-infected CD20-positive B-cell lymphoma undergoing rituximab combination chemotherapy. Am J Hematol. 2008;83(1):59-62.