Hepatitis C Virus Load Kinetics and Clinical Outcome in Patients with Hematological Malignancies: Comparative Study of Autologous Bone Marrow Transplantation and Intensive Chemotherapy

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Introduction

It is estimated that over 170 million people suffer from HCV infection worldwide.[1] The prevalence of HCV infection in patients with cancer ranges from 1.5% to 32.0%.[2] Chronic HCV infection in patients with cancer causes significant additional morbidity and mortality and can interfere with cancer treatment.[3] Over the past two decades, considerable evidence has accumulated with regard to the association between HCV and several hematologic malignancies, most notably B-cell NHL.[4]

The natural course of HCV infection can be altered by cancer treatment. Previous studies have reported a high proportion of chemotherapy discontinuation among patients with cancer with HCV infection and hepatic flares. Damaged liver function after chemotherapy in HCV-infected patients may be related to immunosuppression and HCV reactivation. However, the mechanism of liver injury is still unclear. Poor outcomes may be attributed to hepatotoxicity in patients with underlying hepatitis C or worsening of hepatitis C because of increased HCV replication.[5]

Hematopoietic stem cell transplantation (HCT) improves outcomes in patients with hematologic malignancies. However, the hepatic, extrahepatic, and oncologic outcomes of HCV infection in HCT recipients have yet to be systematically characterized. The occurrence of infection with HCV in patients undergoing HSCT poses several clinical problems, as it can jeopardize the ultimate prognosis, owing to the possibility of progression to fulminant hepatic failure and also the possible evolution to chronic active hepatitis, liver cirrhosis, or hepatocellular carcinoma.[6]

Aim of the work

The aim of this work was to evaluate the impact of the autologous bone marrow

transplantation and intensive chemotherapy on viral load kinetics of HCV patients and correlate it with the clinical outcome.

Patients and Methods

This is a prospective, cohort study conducted on thirty patients with hematological malignancies (including Hodgkin's lymphoma, Non-Hodgkin's lymphoma and Multiple Myeloma) and proven infection with HCV. The study was carried out on Egyptian patients attending El-Maadi Armed Forces Medical Compound, Cairo, Egypt. Patients age range was 18 - 55 years. All patients had child A score liver cirrhosis. Written consent was obtained from every patient.

All patients were subjected to full history taking, thorough clinical examination, basic laboratory parameters including serum bilirubin (total and direct), serum level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum albumin and prothrombin activity.

The patients were divided into 2 groups Group I included 15 patients who received intensive chemotherapy, i.e., (DHAP, DEHAP, ESHAP) for 3-4 cycles with measurement and recording of HCV RNA viral load by PCR before the 1st cycle and then every 10 days through the other cycles. Group II included 15 patients who received autologous BMT with measurement and recording of HCV RNA by PCR before the conditioning regimen and then every 10 days

Statistical Analysis

The statistical analysis of data was done using ***SPSS*** program (SPSS, Inc, Chicago, IL) version 20. Qualitative data were presented as frequency and percentage. Chi square or Fisher's exact tests were used to compare

groups. Quantitative data were presented as mean, standard deviation, median and range. The quantitative data were examined by Kolmogrov Smirnov test for normality. For comparison between two groups; student t-test, and Mann-whitney test (for non parametric data) were used. P-values of <0.05 were considered significant.

Results:

There was no significant difference between the two study groups as regard personal data or clinical data (Table 1 & 2)

Table 1: Comparison between study groups as regard of personal data

		Group				P
		Chemotherapy		BMT		
		Mean	±SD	Mean	±SD	
Age		35.3	11.3	38.0	11.1	0.508
Sex	Male (n %)	8	53.3%	11	73.3%	0.256
	Female	7	46.7%	4	26.7%	

SD: standard deviation

Table 2: Comparison between study groups regarding diagnosis and response to therapy

		Group				P
		Chemotherapy		BMT		
		N	%	N	%	
Diagnosis	MM	0	.0%	1	6.7%	0.700
	HD	4	26.7%	5	33.3%	

	NHL	11	73.3%	9	60.0%	
Response	CR	15	100.0%	14	93.3%	1.0
	PR	0	.0%	1	6.7%	

CR: complete response; PR: partial response

As regard alanine aminotransferase (ALT) level, the pretreatment level was significantly higher among BMT group, while in the post treatment level no significant difference was detected between the two groups. The net change (increase) in ALT due to treatment was higher among chemotherapy group as the mean increase was 17.5±12.6 compared to mean of 14.7 for the BMT group cases.

Table 3: Comparison between study groups regarding change in ALT

	Group						**P**
	Chemotherapy			**BMT**			
	Mean	**±SD**	**Median**	**Mean**	**±SD**	**Median**	
Pre-ALT	25.9	8.8	23.0	32.9	9.4	29.0	0.04
Post-ALT	43.5	11.5	43.0	47.5	15.0	44.0	0.934
ALT Rise	17.5	12.6	21.0	14.7	10.1	13.0	0.046

ALT: alanine aminotransferase; SD: standard deviation

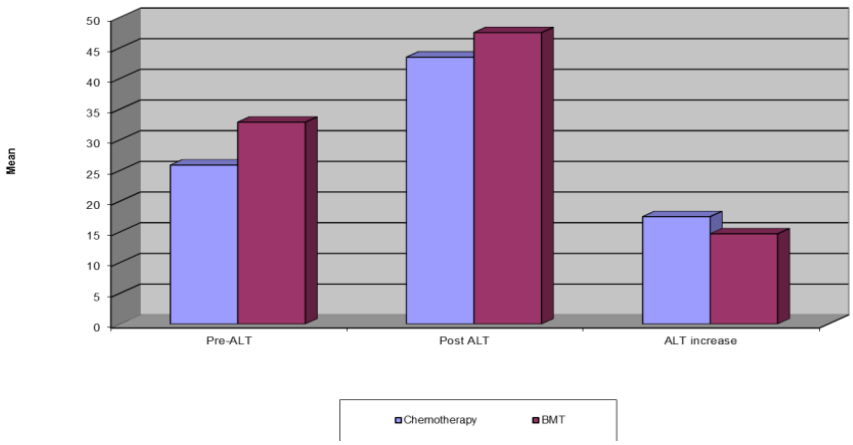

Figure 1: Comparison between study groups as regard ALT level

As regard PCR values, the pretreatment level showed no significant difference between 2 groups, for the post treatment levels, same results were found. Similarly, the net change (decrease) in PCR RNA value due to treatment showed no significant difference between the 2 study groups

Table 4: Comparison between study groups as regard of quantitative PCR

	Group						P*
	Chemotherapy			BMT			
	Mean	±SD	Median	Mean	±SD	Median	
Pre-HCV RNA	13333.3	12737.3	10000.0	12733.3	13073.8	10000.0	0.900
Post-HCV RNA	5600.0	6511.5	.0	3400.0	5487.6	.0	0.325
PCR decrease	7733.3	11584.9	7000.0	9333.3	11043.2	8000.0	0.491

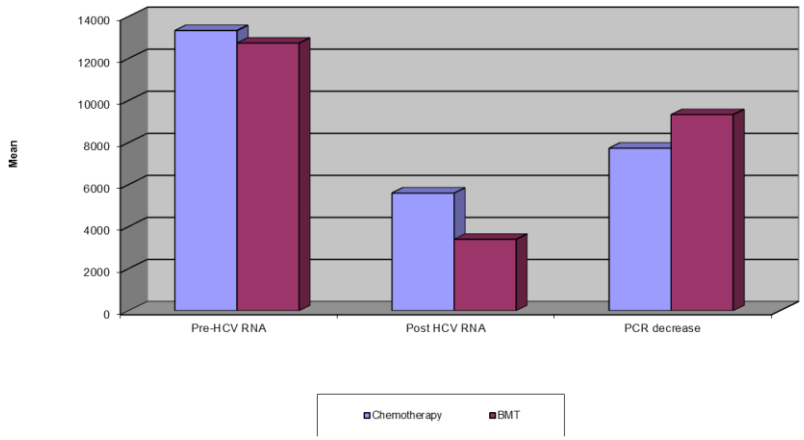

Figure 2: Comparison between study groups as regard of quantitative PCR

Discussion

Hepatitis virus reactivation has been reported in patients treated with systemic chemotherapy or immunosuppressive therapy, and in patients undergoing hematopoietic stem cell transplantation (HSCT).[7] The pathogenesis of hepatitis virus reactivation is not fully understood, though it is generally divided into three stages. Following induction of immune suppression, viral reactivation starts with an increase in replication. After treatment discontinuation, the immune system recovers and attacks infected hepatocytes. Ultimately, hepatitis resolves, and viral replication returns to baseline levels during the recovery stage.[8]Several HSCT studies involving HCV patients have examined early post-HSCT liver complications, survival post-HSCT and pre-HSCT risk factors for post-HSCT liver injury. Most of those studies involved allogeneic-HSCT patients only, and similar studies of autologous stem cell transplantation (ASCT) recipients are scarce.[9]

In this study, we sought to determine the outcome of HCV seropositive lymphoma and myeloma patients undergoing either chemotherapy or ASCT, with regard to changes in alanine aminotransferase (ALT) level pre- and post-exposure to chemotherapy or ASCT, and changes in viral load as measured by HCV-RNA level.

In this study, patients in the chemotherapy arm showed elevation in the ALT level post-chemotherapy as compared to pre-chemotherapy level. Several studies investigated the occurrence of hepatitis as a clinical outcome in HCV- infected patients treated with systemic chemotherapy or immunosuppressive therapy. Some previous studies revealed that HCV-infected patients had a high prevalence of hepatitis. Zuckerman et al. reported that 18 of 33 (54 %) HCV-infected patients had

hepatitis, compared with 36% of non-HCV-infected patients undergoing chemotherapy for hematologic malignancies.[10] Ennishi et al. reported corresponding values of 27 % and 3%, respectively.[11]

Other studies have suggested that the incidence of hepatitis in HCV-infected patients under pharmacological immunosuppression does not differ from that of non-HCV-infected patients**.**[5,12] This discrepancy in the incidence of hepatitis could be due to differences in the patient populations. In the study by Ennishi et al., 43% and 15% of patients had chronic hepatitis and liver cirrhosis, respectively. In HCV-infected patients who do not undergo pharmacological immunosuppression, the incidence of spontaneous hepatic flare is 2% to 40%**.**[13,14]

In this study, patients in the chemotherapy arm showed reduction in the HCV-RNA level post-chemotherapy as compared to pre-chemotherapy level. Various studies studied HCV outcome on the basis of abnormal ALT level without HCV-RNA data. Those studies left open the question of whether the increase in ALT level was related to increase in HCV replication. However, the relationship between increase in HCV-RNA and transaminase elevation is poorly investigated. Morrow et al. showed that nine of 36 (25%) HCV positive patients who received chemotherapy developed elevated liver enzymes, but their study did not evaluate HCV load.[12] In a more recent study, approximately 50% of cases of HCV reactivation were not accompanied by a significant increase in ALT and would have been missed without prospective monitoring of HCV-RNA levels.[15]

These findings suggest that the elevation of transaminase might not be related to viral reactivation but direct liver toxicity from cytotoxic agents. Certain chemotherapeutic agents are known to cause drug-induced liver injury, and caution is recommended with their use in patients with preexisting liver fibrosis. For instance, significant elevation of serum transaminases has been reported in patients receiving anthracyclines (40%), taxanes (50%), vinca alkaloids (5%-10%), methotrexate (15%-50%), erlotinib (10%), pazopanib (50%), and ruxolitinib (25%)**.**[16]

Enhanced HCV replication can occur to a considerable degree in patients who receive chemotherapy or immunosuppressive therapy, but it may not lead to clinically significant sequelae, such as severe hepatitis or hepatic decompensation. However, clinicians should always consider the possibility of HCV reactivation in HCV-infected patients, especially in the face of pharmacological immunosuppression. Further prospective studies on the clinical outcome of enhanced HCV replication during chemotherapy and immunosuppressive therapy are warranted.

The common HSCT-related causes of liver dysfunction are conditioning-regimen hepatotoxicity, toxicity due to antibiotics or antifungal drugs and virus reactivation. Advances in treatment of hematological malignancies with monoclonal antibodies, chemotherapeutic drugs and HSCT have led to an increased incidence of reactivation of hepatitis in HCV patients**.**[5]

In this study, patients in the HSCT arm showed elevation in the ALT level post- HSCT as compared to pre- HSCT level. Data derived from an Italian multicenter study show some interesting differences in the ALT profiles following autologous and allogeneic HSCT. In HCV positive cases, ALT elevation was more frequent, severe and protracted following allogeneic graft compared to autologous transplant. When the course of reactivation was benign, recovery from liver disease was more frequently seen in allogeneic compared to autologous HSCT. Therefore in HCV infection other factors may influence the profile of liver disease, such as immune suppression, conditioning regimen and GVHD prophylaxis, donor immunity and, possibly, the GVH reaction.[17]

In this study, patients in the HSCT arm showed reduction in the HCV-RNA level post- HSCT as compared to pre- HSCT level. Although this is a new finding in HSCT recipients, the literature contains reports about loss of HCV seropositivity post-HSCT. In a study done at MD Anderon, Kyvernitakis et al.

noticed that 13% of the infected patients no longer had HCV antibodies after transplant.[18] Similarly, HCV sero-conversion has been reported in immune-compromised patients, such as HCV-HIV coinfected individuals.[19] A possible explanation of this finding may be related to recovery of the immune system following engraftment. During this period, the immune system attacks the infected hepatocytes. Elimination of infected cells by immune clearance is thought to occur within 2–70 days. However, this remains speculative which raise the need for conducting more studies with larger number of patients to confirm or refute this impressive finding.

Conclusion

We conclude that liver dysfunction that may result from cancer therapy in patients with HCV infection can be predicted and managed without deferring treatment. Monitoring of

HCV-RNA load by PCR could be helpful in guiding treatment of these patients and for detecting candidates who would benefit from DAAs.

Conflict of interest: the authors have no conflicts of interest

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