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Response to Directly Acting Antiviral Drugs in Chronic HCV Egyptian Patients Recovered from Low Grade B-Cell Non Hodgikan Lymphoma

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ABSTRACT

HCV is a lymphotropic virus that infects B-cells promoting favorable conditions for B lymphocyte proliferation. As a consequence, several lymphoproliferative disorders have been associated with the virus. Recently approved direct acting antiviral (DAAs) agents have revolutionized the treatment of chronic HCV infection, and will significantly improve the outcome of HCV associated B-NHL.our study aimed at evaluating the response of DAAs on HCV positive patients with NHL after complete chemotherapy of lymphoma. In this research, we evaluated 100 patients with chronic HCV infection with or without history of lymphoma after giving DAAs for 12 weeks. Both groups had 100% sustained virological response (SVR) at week 12 after treatment, while 96% of patients with history of lymphoma had SVR at week 24 in comparison to 100% SVR in the chronic HCV group, Moreover, 96% of patients had no relapsed lymphoma after treatment by DAAs. And hence, From the previous study we conclude that DAAs significantly improve the outcome of HCV associated B-NHL yet no significance difference was noted regarding SVR.

Keywords: Hepatitis C virus, Directly acting antiviral drugs, Non-hodgkin lymphoma, sustained virological response.

INTRODUCTION

Chronic hepatitis C is a global health problem affecting more than 180 million people worldwide. Egypt possesses the highest seroprevalence of HCV in the world, affecting nearly 15% of individuals aged 15–59 years. (1) Hepatitis C viral infection causes chronic hepatitis and is a major cause of liver cirrhosis and hepatocellular carcinoma. (2) HCV infects B-cells promoting favorable conditions for B lymphocyte proliferation. As a consequence, several lymphoproliferative disorders have been associated with the virus, including mixed cryoglobulinemia (MC) and Bcell non-Hodgkin lymphoma (B-NHL). (3) In Egypt, non Hodgkin's lymphomas ranks as the fifth most common cancer in both the sexes. Chronic HCV infection is known to be associated with both B cell indolent, as well as aggressive lymphomas. HCV associated lymphomas include the following histological subtypes: Marginal zone lymphomas (MZL) which is the most common type of HCV associated B-NHL subtype accounting for approximately 12% of all B-cell lymphomas. (4) and is categorized into three different sub-types: (i) Extra nodal MZL marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type;(ii) Nodal marginal zone lymphoma (NMZL); and (iii) Splenic marginal zone lymphoma (SMZL), Lymphoplasmacytic lymphoma (LPL) is a rare type of HCV related B-cell NHL. (5) DLBCL is another rare type of NHL yet it is the most common lymphoma subtype associated with HCV infection in western countries (6).

Recently, many experimental studies explained the molecular mechanisms of HCV-mediated B-cell proliferation and transformation to NHL. (7)

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HCV eradication by antiviral therapy (AVT) is associated with complete regression of lymphomas; chemotherapy followed by AVT is the main line of treatment of aggressiveLymphomas. (8, 9) In the past few decades, the anti-proliferative and immunomodulatory effects of interferon played an important role in remission of lymph proliferative disorders. (10) yet, the deleterious side effects caused by IFN treatment and its parentral route of administration had limited its effects and exclude a low-tolerability group from treatment, such as advanced age, presence of liver cirrhosis, or other co morbidities including HCC. And hence, the use of recently approved DAAs has revolutionized the treatment of HCV infection, leading to an SVR approaching 100% for all genotypes and good tolerability for all cases. (11) Therefore, we aimed at evaluating the response of DAAs on HCV positive patients with NHL after complete chemotherapy of lymphoma..

SUBJECTS AND METHODS

This Study is a prospective observational study conducted on 100 Egyptian patients with chronic HCV infection with or without history of lymphoma seen at Clinical Oncology and Tropical Medicine Departments, Alexandria University from October 2015, to December 2016.

Patients are divided into two groups: group 1 included: 50 patients recovered fromLymphoma with chronic HCV infection and group 2 consisted of 50 patients with chronic HCV infection without lymphoma as a control group.

HCV infection was defined as detectable HCV RNA in the serum. Patients with active lymphoma, solid tumor, other hepatotropic viruses and human immune deficiency virus were excluded from this study.

All information regarding patient's demographics,clinical characteristics, liver profile, were collected. All patients were given Antiviral treatment triple regimen (sofosbuvir , daclatasvir and weight based ribavirin) for 12 weeks and this was in accordance with the Egyptian guidelines for HCV treatment November 2015, The study was conducted in accordance with ethical guidelines of the declaration of Helsinki and an informed consent will be obtained from every patient included in this work.

Follow up after giving DAAS was done at 12 weeks followed by 24 weeks. Clinical examination was carried out at each visit, as well as haematological, biochemical investigations and abdominal U/S. Compliance to DASS was confirmed by interviewing the patients, PCR was done at week 12 and at week 24.CT guided Lymph node biopsy was done in patients with relapsed lymphoma to confirm diagnosis. Efficacy of DAAS therapy was evaluated in the terms of the presence of SVR defined as absence of HCV RNA in serum 12 weeks after completion of DAAs therapy.

Patients were monitored for the development of adverse effect through the duration of DAAs therapy and after three months of antiviral treatment.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent.The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. The used tests were Chi-square test, Fisher's Exact, Student t-test,4 - Paired t-test, Mann Whitney test and Wilcoxon signed ranks test.

RESULTS AND DISCUSSION

Patient Demographic Characteristics:

The ages of patients in group (I) ranged from 44 to 70 years, with a mean of 58.40 ± 6.59, while ages of patients in group (II) varied from 30 to 57years with a mean of 44.36 ± 7.30. There was statistical significant difference between the two studied groups (P<0.001).

Regarding sex, the majority of patients were males consisting 56.0% of patients in groups I, while in group II the majority of patients were females consisting 64.0%. There was statistical significant difference between the two studied groups (P= 0.045). (Table-1)

Table-1. Comparison between the two studied groups according to demographic data

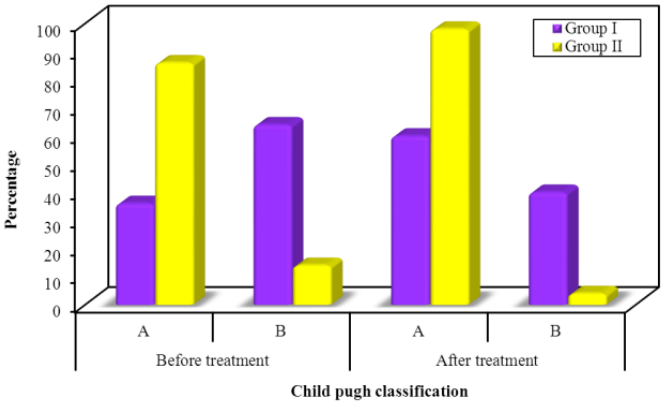
	Group I (n=50)		Group II (n=50)		Test of sig.	P
	No.	%	No	%		
Sex						
Male	28	56.0	18	36.0	□□□ □□□□□	0.045*
Female	22	44.0	32	64.0		
Age (years)						
Min. – Max.	44.0 – 70.0		30.0 – 57.0			
Mean ± SD.	58.40 ± 6.59		44.36 ± 7.30		t=10.097	<0.001*
Median	60.0		47.0			

χ2, p:χ2 and p values for Chi square test for comparing between the two groups
t, p: t and p values for Student t-test for comparing between the two groups
*: Statistically significant at p ≤ 0.05.

Child-Pugh Classification of Both Groups:

In group I, 36% of the patients were Child A, &64% were child B (mean of the score was6.88 ± 0.92), while in group II 86% of the patients were child A and 14% were child B (mean of the score was 5.64 ± 0.83). A significant difference was noted between the child pugh score of group I in comparison to group II. (p<0.001*) (Figure-1).

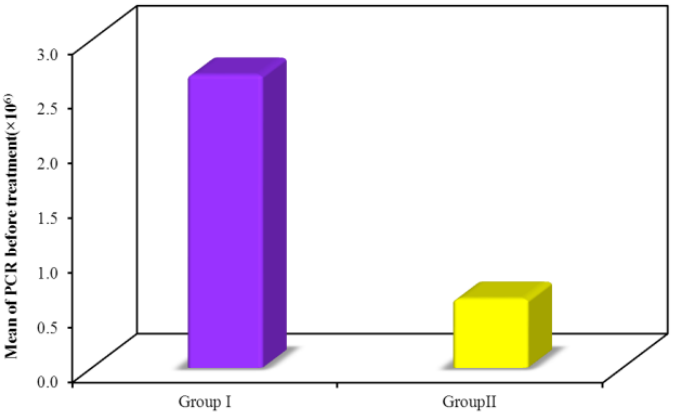
Figure-1. Comparison between the two studied groups according child classification.



Viral Load before Treatment:

Before treatment, viral load in group I ranged from 0.73 to8.08 (10^6 IU) with a mean of 2.68 ± 2.23 IU, while in group II it ranged from 0.01 to2.30 (106 IU) with a mean of 0.63 ± 0.53 IU. The level of Viremia was significantly higher in group I in comparison to group II ($p<0.001^*$). (Figure-2).

Figure-2. Comparison between the two studied groups according to PCR before treatment.



Types of HCV Related Non Hodgkin Lymphoma (NHL) In Group 1 (Figure-1):

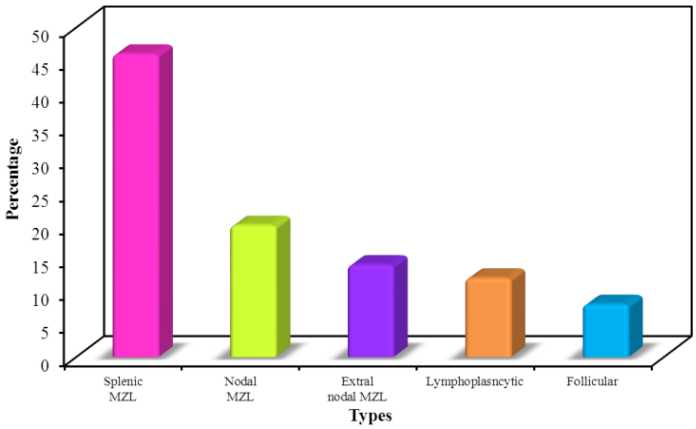
Splenic marginal zonal lymphoma (MZL) was the most frequently encountered type of lymphoma and was found in about 46.0% of patients followed by Nodal MZL noted in about 20.0% of patients, 14.0% had Extra nodal MZL , 12.0% had Lymphoplasmocytic lymphoma and only 8.0% had Follicular Lymphoma (Figure-3).

Follow Up After the End of Treatment

A. Comparison of Child-Pugh scores before and after treatment (figure-3):

There was statistical significant improvement of Child pugh score in both groups after treatmentof DAAs ($p<0.001^*$) respectively(Figure-3)

Figure-3. Distribution of the studied cases according to types of NHL lymphoma related to HCV.



B. SVR (sustained virological response) at weeks 12 and 24

Regarding SVR at weeks 12and 24, at week 12 it was 100% for both groups however at week 24 it was 96% in gp I and 100% in gp II with no statistical significant difference (p=0.495) (Figure-4).

Figure-4. Comparison between the two studied groups according to SVR.

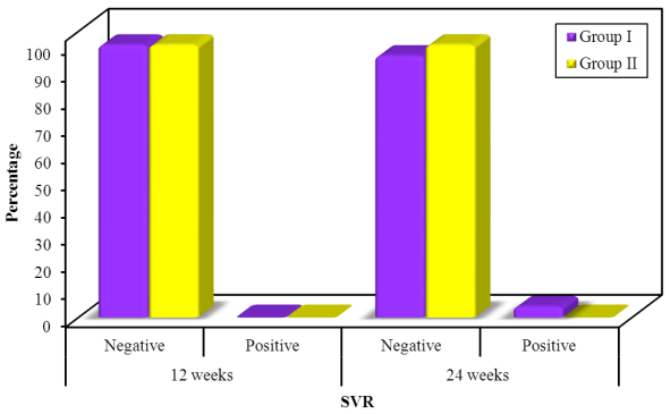
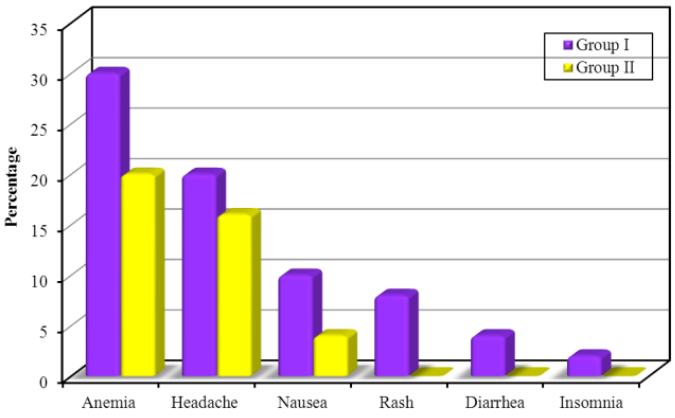


Figure-5. Distribution of adverse effects of DAAs in the two studied groups.



C. Adverse effect of DAAs:

In group I, The most frequent side effects encountered were Anemia in (30%) of thePatients, Headache (20%), Nausea was noted in (10%), skin Rash (8%), Diarrhea (40%), and Insomnia (2%) of patients. However In group II, it were Anemia in (20%) of the patients, Headache (16%), Nausea (4%) of patients& no Rash, Diarrhea, or Insomnia were noticed (Figure-5).

D. Disease free survival (DFS)

4% of patients suffered a relapse of lymphoma. Regarding the types of relapsedLymphoma 50% of cases were having splenic MZL and 50% had Nodal MZL. (Figure 6&7).

Figure-6. Distribution of the studied cases according to DFS in cases group (n=50).

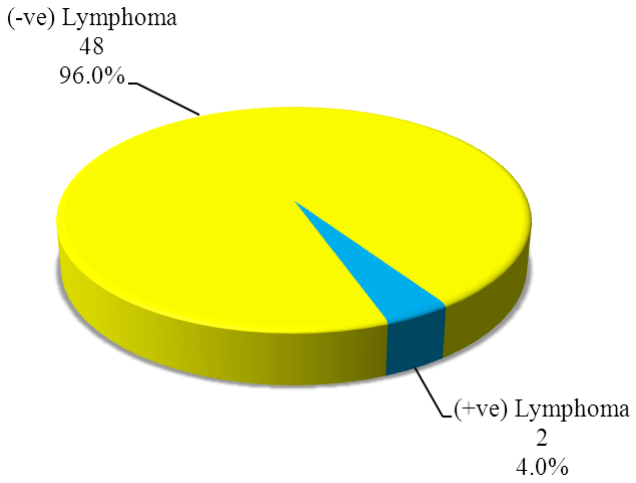
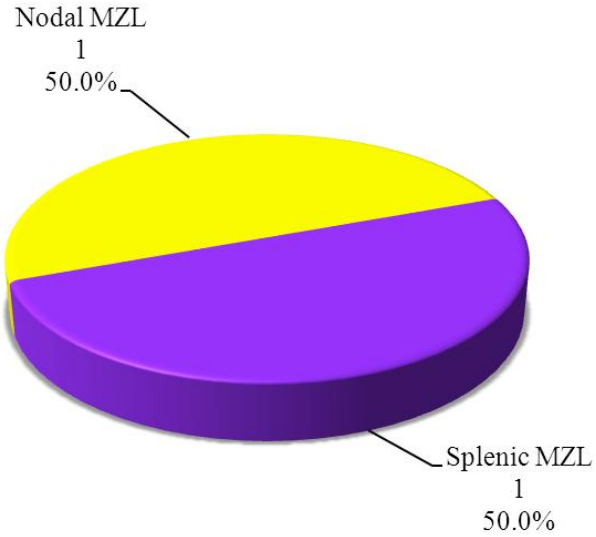


Figure-7. Types of relapsed lymphoma



DISCUSSION

Chronic HCV infection is known to be associated with several lymphoproliferative disorders.[11]Nonhodgkin's lymphoma is considered one of the common extra-hepatic manifestation of HCV infection.[12] Persistent B cells stimulation by HCV usually causes a selection of a B lymphocytes clone forming monoclonal immunoglobulins. Many researchers have postulated that HCV antiviral treatment promotes hematological responses and improve long term patient survival.[13,14] In this context, we lack data concerning the safety and efficacy of different DAAS and hence ,we conducted this study aiming at evaluation of safety and efficacy of sofosbuvir-daclatasvir regimen on HCV positive patients with non-Hodgkin lymphoma after completion of chemotherapy, moreover, studying its effects on lymphoma recurrence.

The present study revealed that Splenic MZL is the most common subtypes of NHL related toHCV and this is in agreement with the results of Bonnet et al.[15]who reported that Splenic marginal zone lymphoma was the most frequently encountered type of lymphoma with HCV infection. On the other hand, Torres HA et al. reported that DLBCL (62%) was the most common HCV related B-NHLs, followed by follicular lymphoma (13%) and MZL (11%) .[16]This difference might be related to the larger number of patients in their studies, or to racial differences. Concerning child pugh classification there was statistically significant improvement in both groups and this is in agreement with Mohamed et al.[17] who reported improvement of child pugh score after treatment by DAAs,this supports the concept that intrahepatic inflammation directly contributes to reduction in liver functions and that blocking inflammation by DAAS therapy could play a role in restoration of liver functions. Regarding SVR, we reported that SVR of 100% in both groups at week12 of treatment, this was in agreement with Gragnani et al[18] Who reported an SVR of 100% while using different SOF based regimen. However, it is in disaccordance with Bonacci Met et al.[19] who reported an SVR of 94% at week 12 in the lymphoma group while, SVR at week 24 was 96% in group I, and 100% in group (II).

Concerning the safety of the DAAs regimen used in this study, The most frequently encountered side effects were Anemia (30%), followed by headache (20%),Nausea (10%), Rash in (8%),Diarrhea in (40%), and Insomnia in (2%) of patients ,This was in disagreement with Sherigar JM et al[20]who reported that, Fatigue was the most common adverse event recorded (32.5%), followed by anemia (19.6%), leukopenia (11.7%), thrombocytopenia (10%), skin rash (8.3%), and headache (7.9%), which may be explained by the use of different DAAs regimens but in our study we have use triple regimen (SOF, DACL and RIBAVIRIN) only.

Regarding the DFS, there was 96.0% patients cured from lymphoma and 4% of patients had relapsed lymphoma (2.0% had splenic MZL, 2.0 had Nodal MZL). This was in agreement with Sultanik*etal*[21], who noticed complete lymphoma regression after a 12-wk regimen with SOF and Daclatasvir (NS5A inhibitor).

CONCLUSION

From the previous study we can conclude that DAAs significantly improve the outcome of chronic HCV associated B-NHL, presence of lymphoma have no influence on SVR in patients on DAAs therapy. We do recommend other researches to be held using different regimens of DAAS.

Conflicts of Interest

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

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