The Egyptian Journal of Hospital Medicine (October 2022) Vol. 89, Page 4540- 4543

Lymphoid Malignancies and Direct-Acting Antivirals: Review Article

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ABSTRACT
Hepatotropic virus HCV, which can infect hepatocytes, is also lymphotropic and can infect lymphocytes as well. Epidemiological, clinical, and biological evidence suggests that the pathogenesis of at least a portion of B-cell non-Hodgkin lymphomas (NHLs) are related to HCV infection. In the last six years, the approval of the new IFN-free antiviral treatment (AVT) with DAAs revolutionized the treatment of chronic HCV infection and many studies show improvement of lymphoid malignancies associated with HCV infection upon the use of direct-acting antivirals (DAAs). DAAs alone can improve indolent lymphomas and DAAs combined with chemotherapy improve the outcome of more aggressive lymphomas as many studies show that patients with HCV infection and lymphoid malignancies usually presented with a higher stage, have a higher frequency of extranodal presentation and a lower response rate (RR), disease free survival (DFS), and overall survival (OS) compared with other patients with lymphoid malignancies without HCV infection.
Moreover, a number of lymphoid malignancies had reported soon after DAAs treatment for HCV infection. This is a systematic review of DAAs and their effect on lymphoid malignancies when given either combined or without chemotherapy. In addition, the review contains all cases reported before for the development of lymphoid malignancies after DAAs treatment for HCV infection.
Keywords: HCV, Lymphoid malignancies, DAAs.

INTRODUCTION

Some infections are related to lymphoma such as The Epstein-Barr virus (EBV) and Hodgkin disease or Burkitt's lymphoma, human T-cell leukemia virus type 1 and adult T cell leukemia and lymphoma, and Helicobacter pylori and lymphoma of the stomach mucosa associated lymphoid tissue [(1)].

EBV-positive diffuse large B-cell lymphoma (DLBCL) and human herpesvirus type-8 (HHV-8)-positive DLBCL are two distinct subtypes of NHL, which related to specific viral infection and classified separately according to the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms [(2)], which means that these types of lymphoma carry different manifestations and prognosis.

Hepatotropic virus HCV, which can infect hepatocytes, is also lymphotropic and can infect lymphocytes as well. Epidemiological, clinical, and biological evidence suggests that the pathogenesis of at least a portion of B-cell non-Hodgkin lymphomas (NHLs) are related to HCV infection [(3)].

HCV was found in peripheral blood mononuclear cells and lymph nodes, indicating HCV infection [(4)]. Hepatitis C NS3 protein was also found in tumor cells in individuals with NHL who were also HCV-infected [(5)]. There is evidence from a meta-analysis that HCV infection increases the chance of getting NHL by 2.5 times [(6)].

Numerous studies demonstrate that when compared to patients with lymphoid malignancies who do not have HCV infection, those with HCV infection and lymphoid malignancies typically present with a higher stage, have a higher frequency of extra-nodal presentation, and have inferior RR, DFS, and OS [(7)]. It is plausible to conclude from this that treating HCV infection will enhance lymphoid malignancy outcomes in people who are also infected with the virus.

IFNa and peg INF plus minus ribavirin (RBV) were once the standard treatments for HCV infection, and numerous studies have shown that using these medications can improve the prognosis for lymphoid malignancies, particularly indolent B cell lymphoma, and that the hematological response is directly related to the viral response [(8)].

However, unfortunately these drugs have a high toxicity profile and a low rate of virology response and the hematological response might be related to the direct anti proliferative effect of INF rather than the virology response [(9)].

The recent approval of the new IFN-free AVT with DAAs transformed the treatment of chronic HCV infection by enabling sustained virologic response (SVR) rates to peak at 100% in all viral genotypes and, importantly, with almost negligible toxicity [(10)].

DAAs lacks the direct anti proliferative effect of interferon [(9)] and improvement of the lymphoid malignancies outcome on these drugs would provide more conclusive evidence of the link between HCV infection and lymphoid malignancies.

Moreover, it has been observed that different types of lymphoid malignancies were diagnosed in patients after treatment with DAAs. It may be just an association or DAAs might have some relation to this. Many studies shows large number of patients who developed

Received: 12/5/2022
Accepted: 19/7/2022

hepatocellular carcinoma (HCC) post DAAs treatment, only case reports described nine patients who developed lymphoid malignancies post DAAs since 2016 until now, other studies shows that DAAs might have an effect on cell-mediated immunity [11-17].

DAAs alone in the treatment of indolent lymphoma:

The association between indolent lymphoma and HCV infection is well established being strongest in splenic marginal zone cell lymphoma (SMZL) and lymphoplasmacytic lymphoma (LPL). With the use of INF based therapy, many literatures show resolution of these types of lymphoma with the eradication of HCV only, without the need for specific anti lymphoma treatment, as in these types of lymphoma specific anti lymphoma treatment can be safely delayed [8].

As regard using DAAs in this setting, the first Italian case report shows SVR and complete hematological response in a patient with both HCV infection and SMZL with the use of DAAs [18]. Following this, numerous other case reports reveal the same outcomes. These findings imply that HCV elimination may be sufficient to cause the regression of indolent NHLs, as HCV-associated MZL can achieve a significant rate of hematological response even with DAAs only.

The prospective, multicenter, phase 2 BArT study (NCT02836925), initiated by the Fondazione Italiana Linfomi, is examining the efficacy of IFN-free DAA regimens in untreated, HCV-positive, non-cirrhotic, indolent NHL patients who do not meet the requirements for receiving immediate traditional anti-lymphoma therapy. SVR was reached in 100% of patients. 45% of lymphoma patients experienced an overall response rate (ORR), with 20% attaining a complete response (CR) and 25% a partial response (PR). These findings indicate that in these patients, first-line therapy should be HCV eradication with DAAs [19].

With the exception of one patient who had decompensated cirrhosis, all patients treated with DAAs experienced a virological response, according to results of a second retrospective multicenter research. The same conclusion as the Italian study was supported by the hematological ORR of 67%, CR in (26%), and PR in (41%) [20].

IFN-free and IFN-based antiviral therapy are compared in patients with indolent B cell lymphoma and HCV infection in another multicenter, multinational comparative study of HCV-associated indolent B-cell lymphoproliferative diseases treated with DAAs [21]. The anti-proliferative impact of IFN in lymphoid malignancies, which was previously employed as an anti-lymphoma medication, explains why IFN is clearly more effective in this study to control lymphoma (greater CR with longer duration of response (DOR) [21]. On the other hand, DAAs are less toxic and more efficient at curing HCV. With both strategies, the OS and progression-free survival (PFS) results are comparable. These findings suggest that this chemotherapy-free strategy should be used as first-line anti-lymphoma therapy in HCV-B-NHL patients who do not require immediate conventional treatment because DAAs showed superior tolerance and a higher SVR.

According to these results, the hepatological (The European Association for the Study of the Liver (EASL)) and hematological (The National Comprehensive Cancer Network (NCCN)) international guidelines recommend starting HCV treatment as the initial therapeutic option in the case of indolent lymphomas associated with HCV infection [22,23].

DAAs combined with chemotherapy in lymphoma treatment:

As mentioned before DAAs can be used alone as 1st line treatment in patients with indolent lymphoma and HCV infection in case that immediate conventional anti-lymphoma treatment is not needed, but some patient might need immediate chemotherapy and also in other types of lymphoma diffuse large B cell lymphoma (DLBCL) chemotherapy treatment can't be delayed. It will be troublesome in this scenario because chemotherapy treatment will have an adverse effect on the patient's immunity, which could increase the HCV viral load and cause liver damage that would affect subsequent chemotherapy treatments [24].

Given the high rate of toxicity of both types of treatment, combining INF and chemotherapy in the past was not practical. However, with the recent approval of highly effective DAAs with minimal toxicity profiles, the combination of these drugs and chemotherapy can be safely examined in patients with lymphoma and HCV infection for the treatment of both HCV infection and lymphoma [25].

Until now, only 7 studies examined the effect of DAAs given concurrently with chemotherapy in patients with different types of lymphoid malignancies and HCV infection [25-31]. Most of these studies are retrospective studies with only 1 prospective study [25]. These studies involved 98 patients who were diagnosed with various forms of lymphoma (mostly DLBCL, follicular lymphoma (FL), and marginal zone lymphoma (MZL)) with persistent HCV infection. They looked at the safety and effects of DAAs administered with chemotherapy either concurrently or after the completion of chemotherapy.

In total, 56 patients got DAAs concurrently with chemotherapy and 42 patients received DAAs post-chemotherapy. In all studies, the SVR ranged from 100 to 82%, and the lymphoma response was outstanding (CR ranged from 100 to 82%). This great outcome persisted even after follow-up spanning from 9 to 34 months [25-31].

Most importantly, there was no additional liver toxicity from the combination, and all patients continued their medication without interruption. These trials demonstrate that the use of DAAs along with chemotherapy, either concomitantly or following the completion of chemotherapy, results in excellent lymphoma and HCV eradication outcomes and is safe.

Lymphoma developed after DAAs:

DAAs markedly revolutionized the treatment of HCV infection but it is noticed that HCC is diagnosed frequently after the end of DAAs treatment even with HCV eradiation. In addition, it is the same for lymphoma. Since 2016 until now, only case reports mentioned 9 cases who developed lymphoma soon after the end of DAAs treatment [(11-17)]. Most cases developed aggressive lymphoma (5 with DLBCL and 2 with aggressive mantle cell lymphoma) and 2 patients developed indolent lymphoma (1 with marginal zone lymphoma and 1 with indolent mantle cell lymphoma), the time period of developing the lymphoid malignancy after the end of DAAs range from 1-19 months.

The underlying mechanisms for this observation is unclear. However, several possible mechanisms have been proposed in recent publications. According to **Andrade *et al.*** [(15)] a survival signal in B cells is brought on by genetic damage brought on by HCV, which may result in late transformation even years after HCV clearance.

Unlike IFN therapy, DAAs cannot directly treat a subclinical cancer or improve an immune response to malignancy [(9)]. Additionally, it has been noted that the persistence of CD4 regulatory T cells, which block cytotoxic CD8+ T cells exposed to B cell NHLs, is linked to the clearance of HCV with DAAs [(32)].

Furthermore, **Reig *et al***. [(33)] proposed that after HCV therapy with DAAs, memory helper T cells established a hypo-responsive condition to tumor antigen, which may leave individuals who defeated HCV infection susceptible to the emergence of malignancies. After HCV clearance with DAAs, it is thus feasible that premalignant B cells with genetic alterations survive by evading immune monitoring, resulting in the transformation of these B cells into malignant clones, such as DLBCL.

Although the precise mechanism, by which DAAs influence tumor growth is yet unknown, a prior clinical investigation found a connection between DAA treatment and serum vascular endothelial growth factor (VEGF) levels. Patients with HCV experienced a roughly 4-fold increase in serum VEGF levels after DAA treatment, and these levels persisted through the completion of the course of therapy [(34)]. Significantly, elevated VEGF expression has been seen in tissues or serum in hematologic malignancies, which speeds up tumor growth by encouraging angiogenesis and vasopermeability [(35)].

All instances who subsequently developed lymphoid malignancies were given antiviral regimens, which included sofosbuvir [(11-17)]. To our knowledge, sofosbuvir has not yet been linked to any side effects that have been associated with lymphomagenesis, despite the fact that it has been shown to be successful in treating HCV-related MZL [(26)]. To determine whether sofosbuvir truly promotes lymphomagenesis, more research is required.

CONCLUSION

We reviewed previous studies, which use DAAs in the treatment of patients with lymphoid malignancies and HCV infection. In conclusion DAAs can be used alone for the initial treatment of indolent lymphoma associated with HCV infection also it can be safely used with chemotherapy without added toxicity and excellent outcomes unfortunately, the development of lymphoid malignancies may occur, even after successful HCV treatment with DAAs. Therefore, clinicians should be aware of such risks during and after antiviral treatment with DAAs.

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