Lymphoma and Other Lymphoproliferative Malignancies

The association with hepatitis C virus (HCV) infection and non-Hodgkin’s lymphoma (NHL) was first recognized shortly after the discovery of the virus[1]. Although numerous studies have confirmed the association, the relative risk for NHL in patients with HCV is still relatively low, consistently in the range of 2-3-fold compared to uninfected populations, which is much lower than the relative risks seen for hepatocellular carcinoma (HCC) in patients with HCV[2]. Interestingly, the risk of NHL appears to be higher in countries with higher HCV prevalence (Egypt, Italy), whereas some low prevalence countries have not found an association at all. The increased risk is seen primarily for B cell lymphomas, particularly marginal zone lymphoma (MZL), but an association has also been reported with diffuse large B cell lymphoma (DLBCL), follicular, chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma and others[3]. Some studies have also reported more aggressive clinical presentations among HCV-associated NHL.

How exactly HCV leads to NHL development is not entirely clear but the relatively strong epidemiological relationship and more importantly, the response of NHL to antiviral therapy, suggest a causal link. Chronic antigenic stimulation of B cells with expansion of clonal populations is the most commonly proposed theory to explain the HCV-NHL link[3]. Monoclonal antibodies from patients with HCV-associated NHL have a restricted repertoire of the variable immunoglobulin region, which expand upon exposure to and can even bind the E2 envelope protein of HCV, the primary target of HCV antibody responses[4]. Interestingly, patients with HCV associated mixed cryoglobulinemia (MC) have similar clonal populations of B cells prior to the emergence of lymphoma. It has therefore been proposed that, like in H pylori infection, B cells proliferate in response to HCV and in some patients these chronically proliferating populations clonally expand and ultimately lead to NHL[2]. Because most patients with cryoglobulinemia do not develop NHL, it is likely that a second hit is required. Translocations in the anti-apoptotic Bcl-2 gene have been identified in patients with HCV-associated MC and NHL, however it is not clear whether these occur spontaneously or in response to HCV directly. The t(14:18) translocation has been proposed as a possible biomarker for identifying those at risk of NHL[5]. Other theories including B cell proliferation via the HCV entry factor CD81 and direct infection of B cells have been proposed, but to date a clear understanding of the HCV, MC, NHL link is missing[3]. It is likely that other genetic or environmental factors are also required and may account for the relatively modest increased risk of NHL and possibly for the wide geographic differences in incidence.

Perhaps the most convincing evidence linking HCV and NHL is the response to antiviral therapy. The initial report by Hermine and colleagues[6] showed complete remission of splenic lymphoma with interferon-alpha therapy in HCV-infected individuals with no response in those without HCV. Subsequently others have reported similar data with good correlation between antiviral and NHL responses. Patients who received NHL treatment have shown lower relapse rates if they subsequently were able to clear HCV with antiviral therapy[7]. In patients with
aggressive lymphoma, antiviral therapy must be delayed until the NHL is under control. Rituximab-based chemotherapy has become the first-line approach to treating aggressive B cell lymphomas. Although hepatotoxicity has been reported at higher frequency in patients treated for HCV-related NHL, some of the data are hard to interpret because of the definitions for hepatotoxicity used[3]. Although there have been infrequent reports of HCV ‘flares’ during chemotherapy[8], most data suggest that HCV does not ‘reactivate’ like HBV and chemotherapy should be well tolerated in HCV-infected individuals without cirrhosis. As antiviral therapy improves, it may even be possible to combine HCV treatment with treatment for NHL.

Given the strong association and likely causal link between HCV and NHL, it may be prudent to treat infected individuals to reduce the risk of lymphoma in the future. One Japanese study showed that the annual risk of NHL decreased among HCV-infected patients after successful viral eradication[9]. Because HCV-associated NHL is uncommon, antiviral therapy to prevent NHL should not likely be the sole indication for treatment. However, it may be prudent to target higher risk groups, particularly those with significant cryoglobulinemia, whether symptomatic or not, to both prevent cryo-related disease but also to reduce the risk of malignant transformation.

The data linking HCV with NHL will be reviewed with a focus on how antiviral therapy may alter the risk of HCV-associated NHL.

References