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ID CASES

Concurrent Systemic Chemoimmunotherapy and Sofosbuvir-Based Antiviral Treatment in a Hepatitis C Virus-Infected Patient With Diffuse Large B-Cell Lymphoma

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Hepatitis C virus (HCV) infection is associated with the development of non-Hodgkin lymphomas. For aggressive lymphomas, such as diffuse large B-cell lymphoma (DLBCL), treatment of HCV infection is typically deferred in treatment-naive patients until after completion of lymphoma therapy [1, 2]. We report a case of HCV-associated stage IV DLBCL successfully treated concurrently using chemoimmunotherapy and a sofosbuvir-based antiviral regimen.

Keywords. DLBCL; Hepatitis C Virus; Lymphoma; Sofosbuvir.

CASE

A 45-year-old white male with a remote history of intravenous drug use, soliciting prostitution, and incarceration was seen for several months for treatment of progressive lower back and abdominal pain. His physical exam revealed cervical and inguinal lymphadenopathy but no evidence of cirrhotic liver disease. His clinical evaluation, including computerized tomography, showed the following: submandibular, mediastinal, axillary, abdominal, pelvic, and inguinal lymphadenopathy; mild splenomegaly; and multiple hypodense lesions in the liver and spleen. Excisional biopsy of a submandibular lymph node showed diffuse large B-cell lymphoma (DLBCL) with a small population of grade 3 follicular lymphoma cells, suggestive of underlying transformation. Bone marrow biopsy indicated 2% marrow involvement. Immunohistochemistry revealed populations of malignant cells expressing CD20, BCL-6, BCL-2, and Ki-67. Only follicular cells expressed CD10. Positron emission-computerized tomography (PET-CT) noted extensive hypermetabolic lymphadenopathy above and below the diaphragm compatible with high-grade lymphoma, with a standardized uptake value of 27.6 in the axilla. Based on the extent of his disease, he was staged as IVsA with an International Prognostic Index score of 3 (elevated lactate dehydrogenase, stage IV, greater than 1 extranodal site involved).

Pre-chemotherapy laboratory evaluation revealed hepatitis C virus (HCV) genotype 1a infection with a viral load of 6.74 $\log_{10}$ IU/mL. He had no prior diagnosis of HCV infection, and he had not been previously treated for HCV infection. Testing for hepatitis B virus, human immunodeficiency virus, and syphilis were negative. He started chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in late January 2014, and he completed six 3-week cycles based on current practice guidelines. He was referred to the infectious disease clinic for treatment of his HCV infection, and he began treatment with sofosbuvir (400 mg once daily), weight-based ribavirin (600 mg twice daily), and pegylated interferon (IFN)-α (180 μg once weekly) in March 2014. Although an IFN-free regimen was considered for treatment, IFN-α was used due to a potential benefit in patients with follicular lymphoma [3].

The patient tolerated and clinically responded to concurrent therapy with minimal side effects. He completed 12 weeks of antiviral therapy consistent with Class 1 treatment recommendations at that time [4]. Eight weeks into antiviral therapy, his ribavirin dose was decreased to 200 mg twice daily due to anemia (hemoglobin nadir of 8.8 g/dL) prompting blood transfusions (Figure 1A). He was also admitted for 1 episode of chemoimmunotherapy-associated neutropenic fever, and he therefore received pegfiligastrim with subsequent chemotherapy cycles without further episodes of febrile neutropenia. A 4-week viral load was unavailable because it was lost during shipping to the reference laboratory; however, an 8-week viral load was undetectable. Six- and 12-month viral load were both undetectable, diagnostic of a sustained virologic response (SVR) (Figure 1B). The lymphoma responded to the chemoimmunotherpy as demonstrated by 3- and 6-month post-chemotherapy PET-CTs, which showed no evidence of metabolically active disease. Additional long-term follow up in early 2016 showed (1) no findings consistent with development of new malignancy as well as (2) normal hematologic and biochemical testing.

DISCUSSION

This patient had HCV-associated DLBCL, achieving both complete response and SVR after concurrent chemoimmunotherapy and antiviral therapy using a sofosbuvir-based regimen. To date, 3 published cases have reported successful antiviral treatment in HCV-associated DLBCL using sofosbuvir-based regimens. Carrier

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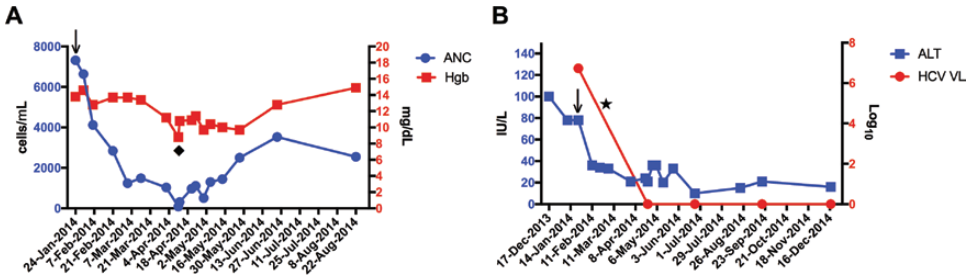

Figure 1. (A) Graphs of absolute neutrophil count (ANC) and hemoglobin (Hgb) over the course of therapy and follow up. (B) Graphs of alanine aminotransferase (ALT) and hepatitis C virus (HCV) viral load (VL) over treatment duration and follow up. (↓) Start date of chemotherapy (24 Jan). (♦) Date ribavirin dose decreased/neutropenic fever (11 Apr). (★) Start date of antiviral therapy (4 March).

et al [5] reported 2 patients who developed SVR with a sofosbuvir-daclatsvir antiviral regimen, but treatment of HCV-infection was initiated only after clinical remission of the lymphoma was declared. Likewise, Romagnoli et al [6] achieved SVR in an HCV-infected patient in remission from DLBCL using sofosbuvir, ribavirin, and IFN. None of the above cases involved treating patients concurrently for their lymphoma and HCV infection.

In contrast to DLBCL, indolent lymphomas, such as splenic marginal zone lymphoma, have demonstrated clinical response solely with the antiviral therapy [7–9]. Clinical response, as in the above cases, has been correlated with achievement of SVR. This was recently echoed in a meta-analysis conducted by Peveling-Oberhag et al [10], who found that achievement of SVR was associated with a higher rate of clinical response to lymphoma (73% response vs 53% response; 95% CI 39–67%; $P < .05$). The benefit of antiviral therapy in patients with HCV-associated DLBCL has also been associated with improved 5-year overall survival rates when compared with those who did not receive treatment for their HCV infection [11, 12].

Although current recommendations defer antiviral therapy until after treatment of DLBCL [2], this patient was treated concurrently using a regimen for treatment-naive patients. The primary concern with concurrent antiviral therapy is the potential for drug-drug interactions or worsened drug toxicities, particularly with ribavirin and IFN. This patient developed grade 3 anemia and grade 4 neutropenia, as marked by his severe neutropenia and neutropenic fever. It is unclear the extent to which the ribavirin and IFN and/or R-CHOP contributed to the development of these side effects, because these adverse effects are well described with both therapies. In a Phase II study of patients receiving R-CHOP for aggressive lymphoma, 91% of patients suffered either anemia or neutropenia as a complication, with 58% developing grade 4 neutropenia [13]. Comparatively, 25% and 33% of patients were reported to have grade 3 or 4 anemia or neutropenia, respectively, with the regimen used to treat this patient [14]. Of note, the previously reported hepatic toxicities seen with rituximab administration in HCV patients was not observed in this patient [15]. Although the patient developed anemia and neutropenia, he tolerated concurrent therapy well. Mahale et al [16] recently evaluated the tolerability of concomitant chemotherapy and antiviral therapy in patients with HCV infection and malignancy. The preliminary data presented in abstract form show a higher rate of hematologic adverse events in patients treated with concurrent chemotherapy and IFN-based regimens when compared with IFN-free regimens (100% vs 44%). Adverse events experienced in the IFN-free patients were attributed to chemotherapy or ribavirin and not to the direct-acting antiviral (sofosbuvir, ledipsavir, simeprevir) agents used.

CONCLUSIONS

In this study, we report a case of successful concurrent treatment of HCV infection and DLBCL that resulted in both complete response and SVR that was overall well tolerated by the patient with short-term adverse hematologic events. Based on our experience, as well as the recently published data, we believe that prospective trials assessing the safety and efficacy of concurrent antiviral and chemoimmunotherapy are warranted, particularly because preferred regimens exclude the use IFN and ribavirin for treatment-naive genotype 1-infected patients. Should concurrent therapy be pursued, patients should be monitored closely for adverse events, particularly hematologic complications.

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