



Concomitant Treatment of Hepatitis C Virus and Diffuse Large B-Cell Lymphoma with Direct-Acting Antivirals in HIV Coinfection: A Case Report

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Abstract

This report describes a case of concomitant treatment of advanced diffuse large B-cell lymphoma with chemioimmunotherapy along with direct-acting antivirals for hepatitis C virus in a patient coinfecting with HIV. The patient tolerated gemcitabine, dexamethasone, cisplatin, and rituximab and achieved sustained virologic response after treatment with ledipasvir/sofosbuvir.

Keywords

hepatitis C virus, diffuse large B-cell lymphoma, direct-acting antiviral, HIV

What Do We Already Know about This Topic?

Research shows that hepatitis C virus (HCV) is associated with diffuse large B-cell lymphoma (DLBCL), with possible maintenance of remission of DLBCL after sequential HCV treatment.

How Does Your Research Contribute to the Field?

This is the first case report to describe treatment of advanced HCV with direct-acting antivirals (DAA) with concomitant treatment of advanced DLBCL in a patient coinfecting with HIV.

What Are Your Research's Implications toward Theory, Practice, or Policy?

This case report recommends that concomitant treatment of HCV and DLBCL is just safe and efficacious as sequential treatment, allowing for a timelier cure.

Although evidence is conflicting, studies demonstrate a 2-fold increased risk of individuals with HCV developing DLBCL.^{1,2} Case studies report that the treatment of HCV may improve and maintain remission of DLBCL. However, in these cases, HCV is often treated in a stepwise approach following chemotherapy in situations where the malignancy is low grade.³⁻⁵ To our knowledge, this is the first case to describe treatment of advanced HCV with direct-acting antivirals (DAA) with concomitant treatment of advanced DLBCL in a patient coinfecting with HIV.

Case Report

Clinical Findings

A 56-year-old Hispanic male with a past medical history of HCV and HIV developed submental and submandibular swelling and pain secondary to lymphadenopathy, associated with fevers, fatigue, diaphoresis, chills, and weight loss of 4 pounds in 1 month. His plasma HIV RNA was undetectable (<20

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Introduction

Hepatitis C virus (HCV) has been associated with extrahepatic manifestations including diffuse large B-cell lymphoma (DLBCL), a common type of non-Hodgkin lymphoma (NHL).



copies/mL) and the CD4 count was 244 cells/ μ L (17.4%) on a regimen of raltegravir, emtricitabine (FTC)/tenofovir disoproxil (TDF), and ritonavir-boosted darunavir (DRV/r).

Fibrotest-Actitest showed severe necroinflammatory activity and severe liver fibrosis (fibrosis score: 0.95, F4) suggesting cirrhosis. The patient was infected with HCV genotype 1a with RNA of 13 236 600 IU/mL. Ultrasound of the right upper quadrant showed echogenic appearance of the hepatic parenchyma compatible with fatty infiltration of the liver without evidence of hepatic mass or ascites. A computerized tomography (CT) scan of the neck showed extensive lymphadenopathy suspicious for lymphoma with hazy infiltration of the surrounding fat suggestive for extracapsular spread. Positron emission tomography imaging showed multiple enlarged lymph nodes at bilateral neck, bilateral axillary, bilateral mediastinal, pericardial, peritoneal, and retroperitoneal lymph nodes consistent with DLBCL. A biopsy of the submandibular lymph node confirmed diagnosis of stage III DLBCL (BCL-2+, CD20+, CD21+, MUM-1+, Ki-67 60%, negativity for BCL-1, BCL-6, CD3, CD4, and CD10).

Clinical Course

Previously planned HCV treatment with coformulated ledipasvir and sofosbuvir (LDV/SOF) was postponed based on National Comprehensive Cancer Network recommendations to initially treat aggressive NHL with chemoimmunotherapy regimens. Antiviral therapy may then be considered in patients in complete remission after completion of lymphoma therapy.⁶ Treatment with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (dose-adjusted EPOCH) with intrathecal methotrexate (MTX) was initiated. Six cycles of EPOCH were completed with only 5 cycles of MTX due to rising aspartate aminotransferase and alanine aminotransferase greater than 3 times the upper limit of normal. Positron emission tomography scan revealed near complete remission of DLBCL, with the exception of 3 lymph nodes in the right inguinal region. Repeat biopsy of inguinal nodes was negative.

After the last chemotherapy session, the patient was clinically stable for 9 months. His HIV regimen was simplified to elvitegravir/cobicistat/FTC/tenofovir alafenamide, and DRV in an effort to decrease pill burden and avoid the drug-drug interaction of LDV/SOF and TDF with DRV/r. Initiation of HCV treatment was again planned. However, due to complaints of severe left upper quadrant pain, treatment was again deferred. One week later, he developed uncontrollable left upper quadrant pain, nausea, subjective fevers, chills, diarrhea, weight loss (12 pounds in 1 month), and malaise.

Repeat CT scan revealed marked splenomegaly and moderate lymphadenopathy in the chest, abdomen, and pelvis, with the largest conglomerate lymph nodes seen in the periaortic and retroperitoneal region. A biopsy of the left retroperitoneal lymph node, right inguinal lymph node, and submandibular lymph node confirmed relapse of DLBCL (CD20+, BCL-2+, BCL-6+, MUM-1+, negativity for CD10, TdT, BCL-1,

and MYC). Treatment of relapsed DLBCL with gemcitabine, dexamethasone, cisplatin, and rituximab (GDP + R) was initiated. After tolerability to chemotherapy was confirmed, simultaneous treatment of HCV with LDV/SOF 90/400 mg was initiated.

Seven days after the initiation of LDV/SOF, he developed a left antecubital abscess with bacteremia and vancomycin was administered. Methicillin-susceptible *Staphylococcus aureus* was isolated from the blood cultures and treatment with nafcillin for 4 weeks was initiated. As a result, the second round of chemotherapy was postponed for 2 weeks until the infection resolved. Treatment with LDV/SOF continued without complication. This event was not considered to be related to antiviral treatment.

He received his first 19 days of treatment with LDV/SOF while receiving inpatient chemotherapy and antibiotics with good tolerability of all treatments. He completed the 12-week course with LDV/SOF and achieved sustained virologic response (SVR) 12 weeks posttreatment. The HIV RNA remained suppressed throughout the course of treatment; the CD4 declined to 77 cells/ μ L (16%). He completed treatment with GDP – R, underwent successful autologous bone marrow transplant, and has been clinically stable for approximately 1 year.

Discussion

A great deal of new information has become available regarding the association of DLBCL and HCV.^{3,5} Evidence suggests an HCV-antigen driven process in lymphoma development, similar to that of lymphoid proliferation. Despite the progress made in understanding this relationship, the exact pathophysiology remains unknown.¹ Although a cause for diagnosis and relapse of NHL in our patient is unidentifiable, he does have multiple risk factors. The risk of NHL is higher in men than in women for unknown reasons. Studies suggest that being overweight may increase the risk of NHL, but further research is needed.⁷ Immune system deficiencies, particularly HIV, may increase the risk of NHL. Fortunately, antiretroviral therapy has reduced this incidence.² Infection with HCV is also a risk factor. Several cases have been reported in which the lymphoma has resolved with eradication of the HCV infection without specific treatment for the lymphoma.⁷ Finally, the risk of HCV-related malignancy is thought to increase with time of HCV exposure.⁷ Our patient is an obese man with HIV and chronic HCV infection, all of which may have had a role in his disease progression and relapse. Prevention of modifiable risk factors may help reduce disease occurrence and severity.

Despite uncertainty behind these associations, promising data come from studies in which HCV antiviral regimens are administered. Gisbert et al⁸ reviewed 16 studies where peginterferon (PEG) with or without ribavirin (RBV) was administered to 65 individuals with concomitant HCV and various lymphoproliferative diseases. Remission of lymphoproliferative disease was achieved in 75% of patients after administration of

antivirals and obtaining SVR12.⁸ Applicability of these results to our case is limited since only 23 patients had a diagnosis of NHL with differing severities of NHL (3 low grade, 20 intermediate, or high grade), and none of the patients were HIV coinfectd. Those with higher grades were treated simultaneously for their lymphoma and HCV, with a number of different chemotherapy regimens being utilized. Fifteen of the 23 patients achieved complete remission of their lymphoma, with no mention of SVR status. Due to the severity, recurrence, and presence of clinical manifestations in our patient, concomitant chemotherapy and HCV treatment were deemed justifiable.

A notable concern is whether chemotherapy for NHL in HCV-infected patients affects the treatment course of HCV. It has been proposed that immunosuppressive therapy, including chemotherapy and corticosteroids, enhances viral replication.⁸ However, in Gisbert review, HCV-infected patients with NHL treated with chemotherapy did not experience liver function test abnormalities.⁸ Our patient's consistently normal hepatic panel during treatment supports this. Since he was also hepatitis C virus (HBV) core antibody positive and HBV-DNA undetectable while on FTC/TDF, rituximab was able to be started without concern of HBV reactivation. The American Association for the Study of Liver Diseases reports that strong and accumulating evidence argues against deferral of treatment for HCV infection because of decreased all-cause mortality and extrahepatic complications including NHL. Therefore, concurrent treatment of HCV and NHL was considered.⁹

Several studies have demonstrated the resolution of NHL after administration of HCV treatment and cure; most treated HCV with PEG and RBV.^{2,5,8} Due to the increasing availability of DAAs, previously published data from the pre-DAA era may not be translatable. Our case contributes to the developing literature due to the utilization of a DAA regimen in an HIV-positive patient. A summary of case reports of DAA use in DLBCL-associated HCV is shown in Table 1. Given that newer DAAs display an excellent tolerability and safety profile, concomitant use with chemotherapeutic agents may be considered as long as drug interactions are accounted for.

Persico et al reported an observational study of 20 HCV1b positive patients with DLBCL undergoing parallel chemotherapy and antiviral therapy with LDV/SOF. They concluded that DAA treatment in conjunction with chemotherapy was safe and effective. Patients were of a different subtype and were HIV negative, but treatment of aggressive lymphomas was well tolerated as demonstrated the lack of differences in adverse events in comparison to a historical retrospective cohort of individuals not undergoing antiviral treatment.⁵ Although the aforementioned literature supports concomitant use of antivirals with chemotherapy, this is the first case report to our knowledge that demonstrates successful treatment of HCV with DAAs in an HIV coinfectd individual with DLBCL. Simultaneous treatment of HCV with SOF/LDV and GDP + R may be safe and effective.

Table 1. Case Reports of DAA Use in DLBCL-Associated HCV.

Case Report	Age, Sex	HIV Status	NHL Type	NHL Stage	Chemotherapy	NHL Response	HCV Genotype	Fibrosis	HCV Treatment	HCV Response
Carrier et al ³	38, male	Unknown	DLBCL	Stage IV	R-ACVBP, then R-VPI6-holoxan MTX	Remission	Ib	F2	(After chemotherapy) SOF + DCV + weight based RBV × 12 weeks	SVR
Carrier et al ³	57, male	Unknown	DLBCL	Stage III	R-ACVBP, then R-VPI6-holoxan MTX	Remission	4	F1	(After chemotherapy) SOF + DCV × 24 weeks	SVR
Rossotti et al ¹⁰	42, male	Negative	SMZL	-	None	Remission	Ib	F0	FDV 120 mg daily, DLV 600 mg twice daily, RBV 1000 mg daily	SVR
Sultanik et al ¹¹	57, female	Negative	MZL	-	None	Remission	3a	-	SOF 400 mg daily + RBV 1000 mg daily × 4 weeks, then SOF 400 mg daily + DCV × 12 weeks (With or within 4 weeks of chemotherapy)	SVR
Alric et al ¹²	-	Unknown	DLBCL	-	R + polychemotherapy	Remission	Ib	F3-4	(With or within 4 weeks of chemotherapy) SOF + RBV	SVR
Alric et al ¹²	-	Unknown	DLBCL	-	R	Remission	Ib	F3-4	(With or within 4 weeks of chemotherapy) SOF + RBV	SVR
Alric et al ¹²	-	Unknown	DLBCL	-	R + polychemotherapy	Remission	Ib	F3-4	(With or within 4 weeks of chemotherapy) SOF + LDV	SVR

Abbreviations: DAA, direct-acting antiviral; DCV, daclatasvir; DLBCL, diffuse large B-cell lymphoma; DLV, delecobuvir; FDV, faldaprevir; HCV, hepatitis C virus; LDV, ledipasvir; MTX, methotrexate; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; R, rituximab; R-ACVBP, rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin, cytarabine; RBV, ribavirin; R-VPI6, etoposide, holoxan; SMZL, splenic marginal zone lymphoma; SOF, sofosbuvir; SVR, sustained virologic response.

Authors' Note

Case reports do not meet US Department of Health and Human Services definition of "research." Therefore, after administrative review by the Brooklyn Hospital Center's institutional review board, ethics approval deemed not required. Informed consent for publication was provided verbally by the patient as per The Brooklyn Hospital Center policy. Consent was recorded electronically and documented in the electronic medical record.


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References

1. Silvestri F, Pipan C, Barillari G, et al. Prevalence of hepatitis C virus infection in patients with lymphoproliferative disorders. *Blood*. 1996;87(10):4296–4301.
2. Giordano TP, Henderson L, Landgren O, et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. *JAMA*. 2007;297(18):2010–2017.
3. Carrier P, Jaccard A, Jacques J, et al. HCV-associated B-cell non-Hodgkin lymphomas and new direct antiviral agents. *Liver Int*. 2015;35(10):2222–2227.
4. Michot JM, Canioni D, Driss H, et al; ANRS HC-13 Lympho-C Study Group. Antiviral therapy is associated with a better survival in patients with hepatitis C virus and B-cell non-Hodgkin lymphomas, ANRS HC-13 lympho-C study. *Am J Hematol*. 2015;90(3):197–203.
5. Persico M, Aglitti A, Caruso R, et al. Efficacy and safety of new direct antiviral agents in HCV infected patients with diffuse large B cell non-Hodgkin lymphoma. *Hepatology*. 2017.
6. National Comprehensive Cancer Network. Non-Hodgkin's Lymphomas. (Version 3.2016). Website. <http://cutensoullymphoma.stanford.edu/docs/nhl.pdf>. Accessed September 25, 2018.
7. American Cancer Society. Non-Hodgkin lymphoma risk factors. Web site. <https://www.cancer.org/cancer/non-hodgkin-lymphoma/causes-risks-prevention/risk-factors.html>. Accessed September 25, 2018.
8. Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Systematic review: regression of lymphoproliferative disorders after treatment for hepatitis C infection. *Aliment Pharmacol Ther*. 2005;21(6):653–662.
9. American Association For The Study of Liver Diseases and The Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C. Web site. <https://www.aasld.org>. Accessed September 25, 2018.
10. Rossotti R, Travi G, Pazzi A, Baiquera C, Morra E, Puoti M. Rapid clearance of HCV-related splenic marginal zone lymphoma under an interferon-free, NS3/NS4A inhibitor-based treatment. A case report. *J Hepatol*. 2015;62(1):234–237.
11. Sultanik P, Klotz C, Brault P, Pol S, Mallet V. Regression of an HCV-associated disseminated marginal zone lymphoma under IFN-free antiviral treatment. *Blood*. 2015;125(15):2446–2447.
12. Alric L, Besson C, Lapidus N, et al. Antiviral treatment of HCV-infected patients with B-cell non-Hodgkin lymphoma: ANRS HC-13 Lympho-C study. *PLoS One*. 2016;11(10):e0162965.