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Antiviral therapy improves overall survival in hepatitis C virus-infected patients who develop diffuse large B-cell lymphoma

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Abstract

Chronic Hepatitis C virus (HCV) infection is associated with increased incidence of non-Hodgkin lymphoma. Several studies have demonstrated regression of indolent lymphoma with antiviral therapy (AVT) alone. However, the role of AVT in HCV-infected patients with diffuse large B-cell lymphoma (DLBCL) is unclear. We therefore analyzed AVT's impact on oncologic outcomes of HCV-infected patients (cases) who developed DLBCL. Cases seen at our institution (June 2004-May 2014) were matched with uninfected counterparts (controls) and then divided according to prior AVT consisting of interferon-based regimens. We studied 304 patients (76 cases and 228 controls). More cases than controls had extranodal (79% v 72%; p=0.07) and upper gastrointestinal (GI; 42% v 24%; p=0.004) involvement. Cases never given AVT had DLBCL more refractory to first-line chemotherapy than that in the controls (33% v 17%; p=0.05) and exhibited a trend toward more progressive lymphoma at last examination compared to controls (50% v 32%; p=0.09) or cases given AVT (50% v 27%; p=0.06). Cases never given AVT had worse 5-year overall survival (OS) rates than did the controls (HR, 2.3 [95% CI, 1.01-5.3]; p=0.04). Furthermore, AVT improved 5-year OS rates among cases in both univariate (median [Interquartile range]: 39 [26-56] *v* 16 [6-41] months, p=0.02) and multivariate analyses (HR=0.21

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AUTHOR CONTRIBUTIONS

Contribution: J.H., P.M. and H.A.T. designed the study; H.A.T. and F.T. treated and observed the patients; R.N.M reviewed the pathology reports; J.H., P.M. and M.P.E. collected and analyzed the data; J.H., P.M., F.T., R.N.M., M.P.E., B.P.G., and H.A.T. provided expert opinion; J.H. and H.A.T. wrote the paper.

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[95% CI, 0.06-0.69]; p=0.01). This study highlights the negative impact of chronic HCV on survival of DLBCL patients and shows that treatment of HCV infection is associated with a better cancer response to chemotherapy and improves 5-year OS.

Keywords

hepatitis C virus; diffuse large b-cell lymphoma; antiviral therapy; overall survival

INTRODUCTION

Hepatitis C virus (HCV) is a known hepatotropic virus associated with development of hepatocellular carcinoma.[1,2] In addition, researchers have found evidence of its lymphotropism in epidemiologic, laboratory, and clinical studies.[3] For instance, epidemiologic data demonstrated a close association between chronic HCV infection and development of B-cell non-Hodgkin lymphomas (NHLs), particularly marginal zone lymphoma, lymphoplasmacytic lymphoma and diffuse large B cell lymphoma (DLBCL).[4-8] Authors reported also the presence of HCV genomic material and alteration of gene expression in lymphocytes of infected patients,[9,10] with persistence of inflammatory responses in these cells long after clearance of the virus by antiviral therapy (AVT).[11] However, the strongest evidence of this association is the clinical regression of indolent lymphoma with AVT administered without chemotherapy (CT).[12-14]

Unfortunately, determining the impact of HCV infection on DLBCL prognosis and the role of AVT in HCV-infected DLBCL patients has been difficult, likely because of the more aggressive nature of this NHL subtype than that of indolent lymphomas, preventing the use of AVT without CT. In two recent review articles,[3,15] the authors concluded that AVT does not play a significant role in DLBCL management in view of contradictory results in a few case series studying the effect of AVT given after CT.[16-19] It should be noted that interferon (IFN) was the main antiviral used in these reports. Importantly, when IFN-based therapy is given after DLBCL diagnosis, the effect of viral suppression on oncologic outcomes is confounded by the direct anti-lymphoma activity of IFN.[20]

To overcome these knowledge gaps, we analyzed herein the effect of AVT on the oncologic outcomes in HCV-infected patients who were given IFN-based therapy before DLBCL diagnosis.

PATIENTS AND METHODS

In this retrospective cohort study, the medical records of patients with HCV infection who developed DLBCL and seen at The University of Texas MD Anderson Cancer Center from June 2004 to May 2014 were reviewed. We only analyzed patients who had a proven infection (detectable HCV RNA in serum and/or a history of AVT). Human immunodeficiency virus-infected patients and those who underwent follow-up for less than 6 months were excluded.

Subsequently, HCV-infected DLBCL patients (cases) were matched with uninfected controls (HCV antibody-negative DLBCL patients) at a ratio of 1:3 (Fig. 1). The matching variables were the year of DLBCL diagnosis, sex, age (±5 years), and Ann Arbor stage (1-2 or 3-4). This study was approved by the MD Anderson Institutional Review Board.

Oncologic parameters

Data on DLBCL characteristics extracted from the patient records at the time of diagnosis consisted of: Ann Arbor Stage, Eastern Cooperative Oncology Group (ECOG) performance score, presence of B symptoms, International Prognostic Index (IPI) score, site of extra nodal involvement, bone marrow involvement, and onset of DLBCL (de novo or transformed). Pathology reports were reviewed by a pathologist at MD Anderson to further classify DLBCL according to immunohistochemistry as germinal center B cell (GCB) or non-GCB. Information on all treatment modalities performed, including CT, radiotherapy, and hematopoietic stem cell transplantation (HCT) as well as AVT and its timing relative to DLBCL diagnosis, was collected.

Transformed DLBCL was defined as either a previous history of indolent lymphoma before DLBCL diagnosis or concomitant mixed/discordant biopsies demonstrating indolent and aggressive lymphoma simultaneously. Based on radiologic findings, the patients with liver, stomach, pancreatic, and/or splenic involvement of DLBCL were combined in the upper gastrointestinal (GI) involvement group. A good performance status was defined as an ECOG score of 0-1, whereas a poor performance status was defined as an ECOG score of 2-4. The low, intermediate and high-risk IPI scores were 0-1, 2-3 and 4-5, respectively. The revised 2007 Cheson criteria were applied to defining response of DLBCL to CT, distinguishing complete response (CR), partial response (PR), and progressive disease (PD). Overall survival (OS) was measured from the start date for CT to the date of the last follow-up examination or death resulting from any cause.[21] Progression-free survival (PFS) was measured from the start date for CT to the date of DLBCL progression or relapse.[21] Disease-free survival (DFS) was applied only to patients who had CR after first-line CT and was measured from the end date for CT to the date of DLBCL relapse.[21]

Infectious parameters

Data on HCV infection characteristics, such as date of HCV infection diagnosis, time from first documented HCV risk exposure to DLBCL diagnosis, HCV RNA viral load and genotype, rs12979860 genotype (previously known as interleukin-28B), prior AVT, and virologic response, were collected.

Sustained virologic response (SVR) was defined as an undetectable HCV RNA viral load at 24 weeks after AVT completion, the virologic endpoint used for patients treated with IFN-containing regimens.[22]

Hepatic parameters

Liver fibrosis status at DLBCL diagnosis and after completion of CT was reviewed. Cirrhosis was identified in the patients using either a liver biopsy or a combination of analysis of clinical manifestations of cirrhosis, radiologic findings, and noninvasive fibrosis

markers (FIBROSpect II test; Prometheus Laboratories, San Diego, CA). Portal hypertension was defined according to a combination of clinical and radiologic signs suggestive of this condition. Progression of cirrhosis was indicated by worsening of the Child-Pugh score from baseline parameters. Acute-on-chronic liver failure was defined as previously reported.[23]

Statistical analysis

Descriptive statistics were used to characterize the study population. The endpoints were oncologic (response to first-line CT, relapse or progression, oncologic response at the last follow-up examination, 5-year OS rate, and 3-year PFS/DFS rates), virologic (SVR), and hepatic (worsening of cirrhosis after CT, and hepatic failure).

To determine the effect of HCV infection on the clinical presentation of DLBCL, we compared the characteristics of categorical variables among cases and controls using generalized estimating equations and the logit link function to account for correlations in the matched groups.

To determine the effect of HCV infection on survival and oncologic outcomes, the patients were further separated into three groups: cases never given AVT, cases given AVT before DLBCL diagnosis, and uninfected controls (Fig 1). We first compared oncologic outcomes between the three groups, and then conducted a two-by-two comparison between each case group and controls, and between the two case groups. The 5-year OS, 3-year PFS, and 3-year DFS rates in these three groups were compared, with the differences evaluated using a stratified log-rank test. Finally, a multivariable stratified Cox regression model was used to determine the association between HCV infection and OS after adjusting for potential confounders.

Furthermore, to determine whether AVT affects the risk of death and adverse oncologic outcomes in HCV-infected patients, the cases given AVT were compared with those never given AVT. Categorical variables were compared using a chi-square test or the Fisher exact test. Survival rates were plotted on Kaplan-Meier curves and compared with the log-rank test. A multivariable Cox regression model was used to determine the effect of AVT on the risk of death after adjusting for potential confounders.

Final results were presented as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) and P values. All statistical tests were two-sided and conducted using the SAS software program (version 9.4; SAS Institute Inc., Cary, NC). P values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics

We identified 94 HCV-infected patients with DLBCL during the study period. We excluded 18 patients for different reasons (Fig 1). We considered the remaining 76 patients to be the cases and included them in our analysis. Most of them were male (70%), white (68%), and had a median age of 59 years (Table 1).

DLBCL characteristics

The majority of the cases had de novo DLBCL (72%) and GCB as the cell of origin (56%). Also, most of the cases had Ann Arbor stage 3-4 disease (80%), no B symptoms (67%), a good performance statuses (71%), intermediate to high-risk IPI scores (64%), para-aortic lymph node involvement (58%), and extranodal involvement (79%), with the upper GI tract as the region the most often involved (42%).

Most cases were given rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as first-line CT (72%) and rituximab-ifosfamide, carboplatin, and etoposide (R-ICE) as second-line CT (58%). Twenty two percent of the cases underwent HCT, and 24% received radiotherapy (Table 1).

Infectious characteristics

Forty-eight cases (63%) were known to have chronic HCV infection before onset of DLBCL, whereas 28 cases (37%) had HCV infection diagnosed at the same time or after cancer was diagnosed. Among patients with available data, most of the cases (77%) were infected for more than 30 years, and half of them (50%) had baseline HCV RNA loads ≥6 million IU/ml. The majority had HCV genotype 1 (73%) and rs12979860 genotype CT (63%).

Only 34% of the cases received AVT before DLBCL diagnosis, 38% of whom had an SVR. The only treatment regimens used before DLBCL diagnosis were IFN-based due to the more recent availability of IFN-sparing regimens. Ten cases (13%) received AVT after DLBCL diagnosis. Six of these patients received IFN-free regimens, and all of them had SVRs (suppl table 1).

Hepatic characteristics

Almost one fourth of the cases (24%) had cirrhosis at the time of DLBCL diagnosis, 72% of whom also had portal hypertension. Only 42% of the cases who underwent liver biopsy had advanced liver disease (METAVIR stages 3-4). Among those who did not have cirrhosis, only 2% developed cirrhosis after starting CT, whereas 56% of the cases with baseline cirrhosis had decompensation of their liver disease after CT (suppl table 1). Only five cases (7%) experienced progression to hepatic failure, all of whom were cirrhotic. Causes of hepatic failure were septic shock with multiorgan failure (n=2), portal vein thrombosis (n=1), stricture of a common bile duct caused by DLBCL (n=1), and hepatotoxicity of CT (n=1).

Effect of HCV infection on DLBCL presentation

After matching the 76 cases with the 228 controls (DLBCL patients not infected with HCV), we did not find significant differences in the two groups regarding lymphoma cell of origin, transformation from a previous indolent subtype, ECOG score, IPI score, presence of B symptoms, regional lymph node involvement, use of R-CHOP as first-line CT, use of adjunct radiotherapy, or frequency of HCT (Table 1).

Although we matched the cases and controls according to stage of DLBCL, more cases than controls had extranodal (79% v 72%; $p = 0.07$), bone marrow (36% v 27%; $p = 0.08$), and upper GI (42% v 24%; $p = 0.004$) involvement. The cases also had a higher rate of cirrhosis at DLBCL diagnosis (24% v 2%; $p < 0.0001$) (Table 1). More cases were seropositive for hepatitis B virus core antibodies (HBcAb) (41% v 5%; $p < 0.0001$) but without any difference in detectable levels of hepatitis B virus DNA between the cases and controls (18% v 11%; $p = > 0.99$).

Comparison of the oncologic outcomes of three DLBCL groups

After further dividing the cases based on their AVT exposure, we analyzed three groups of patients (Figure 1): cases never given AVT (N = 40), cases given AVT before DLBCL diagnosis (N = 26), and uninfected controls (N = 198). Cases never given AVT were more likely than the controls to experience failure of first-line CT (33% v 17%; $p = 0.05$). Similarly, cases never given AVT exhibited a trend toward more progressive disease at the last follow-up examination compared with the controls (50% v 31%; $p = 0.09$) or cases treated with antivirals (50% v 27%; $p = 0.06$). We did not find significant differences in the rate of DLBCL relapse related to AVT exposure after first complete or partial remission (46% in the untreated group, 41% in the AVT group, and 40% in the controls; $p = 0.88$) (Table 2). In terms of 5-year OS, the controls had a better survival than did cases who did and did not receive AVT (65%, 61%, and 57%, respectively; $p = 0.05$) (Fig 2A). The cases given successful AVT (those with SVRs) before DLBCL diagnosis had a better 5-year OS rate than did the untreated cases and controls (80%, 57%, and 67%, respectively; $p = 0.02$) (Fig. 2B). Cases given AVT (irrespective of SVR achievement) and controls did not have significantly better 3-year PFS or DFS rates than did the untreated cases (Figures 2C and 2D).

Comparison of the characteristics of the two case groups

While comparing the cases given AVT (n=26) and cases never given AVT (n=40), both groups had similar infectious, oncologic and hepatic characteristics. Cases given AVT had a trend of higher risk IPI score (37% v 16%, p = 0.17) and METAVIR stages 3-4 on liver biopsy (56% v 20%, p = 0.1). In addition, both groups underwent similar oncologic treatment: they were given R-CHOP as first line CT (77% *v* 86% respectively, $p = 0.27$), underwent further CT after oncologic relapse (46% *v* 43%, $p = 0.81$) and R-ICE was the main regimen used as second line CT (62% *v* 67%, $p > 0.99$). (Table 3).

Effect of HCV infection on OS

To determine the effect of HCV infection on 5-year OS of DLBCL patients, we compared cases never given any AVT (n=40) and their matched controls (n=120). The results of a 5-year multivariable cox regression analysis showed that HCV infection increased twofold the risk of death at 5 years in the cases never given AVT when compared to controls (HR, 2.31 [95% CI, 1.01-5.30]; $p = 0.04$) (Table 4).

Effect of AVT on OS

Compared to cases never given AVT, cases treated with AVT before DLBCL diagnosis had a significantly better OS in univariate analysis (median, 39 months; [interquartile range, 26 56] compared to 16 months, [interquartile range, 6–41], $p = 0.02$) (Table 3) and multivariable cox regression analysis (HR, 0.21 [95% CI, 0.06-0.69]; $p = 0.01$) (Table 4).

DISCUSSION

To our knowledge, this is the largest study to support the negative impact of chronic HCV infection on the survival of DLBCL patients. This analysis is also the first to demonstrate the oncologic benefits of AVT in HCV-infected patients who developed DLBCL, including an association with a better response to CT and improved 5-year OS rates.

In view of the potential risk of the use of rituximab in HCV-infected patients, many research studies were conducted to investigate the impact of HCV infection on the survival of DLBCL patients in the rituximab era, though with contradictory results. For instance, four previous studies[24-27] concluded that HCV infection has no effect on survival of DLCBL patients and only two groups[28,29] found worse OS rates in HCV-infected DLBCL patients (26 and 22 cases respectively) when compared to uninfected controls. Our findings indicate that HCV has a negative impact on the survival of DLBCL patients in the rituximab era. In addition, this study is the largest to demonstrate the significant difference in OS rates caused by HCV infection with adjustment for hepatic (cirrhosis) and oncologic risk factors (IPI score, oncologic cell of origin) for mortality.

Previous reports have studied the effect of AVT on survival in HCV-infected DLBCL patients. Michot and colleagues found a trend toward an association between AVT and improved OS rate in 17 out of 45 DLBCL patients (HR: 0.29 [0.08–1.06], $p= 0.06$).[17] Similarly, Merli and colleagues showed improved OS in 23 out of 581 patients receiving AVT, in a univariate analysis only.[16] However, both groups studied the impact of AVT given after CT and after DLBCL remission, using IFN as the mainstay of AVT. This approach was limited by selecting DLBCL survivors and responders to CT before the use of AVT. Another weakness of this approach was the confounding effect of treatment with IFN, a potent anti-lymphoma agent when combined with rituximab.[20] To eliminate these confounders, we analyzed the effect of AVT on survival only when given before DLBCL diagnosis. Future analyses including HCV-infected patients treated with AVT during or after CT with agents that do not have antineoplastic activity may provide more information on the oncologic benefit of AVT.

Primary refractory DLBCL constitutes 15-20% of DLBCL cases in the rituximab era.[30,31] In the present study, we showed that 33% of the DLBCL cases never given AVT had primary disease refractory to CT in contrast with 15% of the cases given AVT and 17% of the controls. This result demonstrates for the first time that DLBCL in HCV-infected patients is more refractory to CT than the uninfected patients but the use of AVT can reverse this refractoriness. This finding may be explained, at least in part, by sustained B-cell activation and B-cell apoptosis inhibition by HCV core proteins in untreated patients.[32-34] On the other hand, patients with untreated HCV may have abnormal hepatic laboratory parameters that

affect the dosing of CT. Abnormal hepatic function may also affect the clearance of some CT agents. Future studies including CT dose intensity analyses will clarify if the refractoriness of HCV-infected patients is attributable to differences in CT or to a sustained lymphomagenic effect of HCV.

Our study emphasizes the importance of HCV screening in cancer centers, as more than one-third of cases were newly diagnosed with active infection at the time of DLBCL diagnosis. We showed previously that 79% of patients with hematologic malignancies and only 7% of those with solid tumors were screened for HCV before CT.[35] Screening more patients will lead to early detection of HCV infection with prompt initiation of AVT to prevent its hepatic and extra-hepatic manifestations.

The major strength of our study was the use of two different strategies to control confounding: matching of cases and controls according to variables influencing survival and adjustment for others, especially cirrhosis, in a multivariate analysis. By matching the cases and controls according to Ann Arbor stage and year of DLBCL diagnosis, the two groups received comparable first line CT and thus we controlled to some extent the confounding effect of CT.

Our study had some limitations. First, as in every retrospective cohort study, it had a mixture of biases, such as selection, and confounding biases, that we overcame by analyzing patients who were given AVT before DLBCL diagnosis only. Second, by studying patients given AVT before DLBCL diagnosis, we may have distorted the association between HCV infection and DLBCL. However, the discovery of persistent inflammatory changes in lymphocytes long after successful IFN-based treatment of HCV infection in addition to alteration of genes expression may explain the presence of lymphomagenesis in patients with apparently undetectable HCV RNA.[11,36,37] Third, we could not analyze the effect of the newer IFN-free regimens mainly because of their recent use, small number of patients, and short duration of follow up to detect survival benefits. In addition, these new drugs were given to few of our patients after DLBCL remission, hence if included we will have an erroneous better survival, biased by an incorrect selection of patients. Finally, observed higher rates of HBV co-infection manifested by higher percentage of HBV core antibody in the HCV-infected group than in the uninfected group. This finding may have impacted the survival of the cases. However, no difference in active HBV viremia was found in both groups.

In conclusion, chronic HCV infection has a negative impact on survival of DLBCL patients. In contrast, AVT is associated with a better response to first-line CT and improves 5-year OS. Our findings support systematic screening and early administration of AVT to any HCV-infected patient. This would not only improve hepatic outcomes as previously shown,[38,39] but also favorably impact patients in whom DLBCL may develop. Larger studies using new direct-acting antiviral agents are needed to validate the survival benefit of AVT in HCV-infected DLBCL patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HCV	Hepatitis C virus
NHLs	non-Hodgkin lymphomas
DLBCL	diffuse large B cell lymphoma

AVT	antiviral therapy
CT	chemotherapy
IFN	interferon
ECOG	Eastern Cooperative Oncology Group
IPI	International Prognostic Index
GCB	germinal center B cell
HCT	hematopoietic stem cell transplantation
GI	gastrointestinal
CR	complete response
PR	partial response
PD	progressive disease
OS	overall survival
PFS	progression-free survival
DFS	disease-free survival
SVR	sustained virologic response
HRs	hazard ratios
CIs	confidence intervals
R-CHOP	rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone
R-ICE	rituximab-ifosfamide, carboplatin, etoposide
HBcAb	hepatitis B virus core antibodies

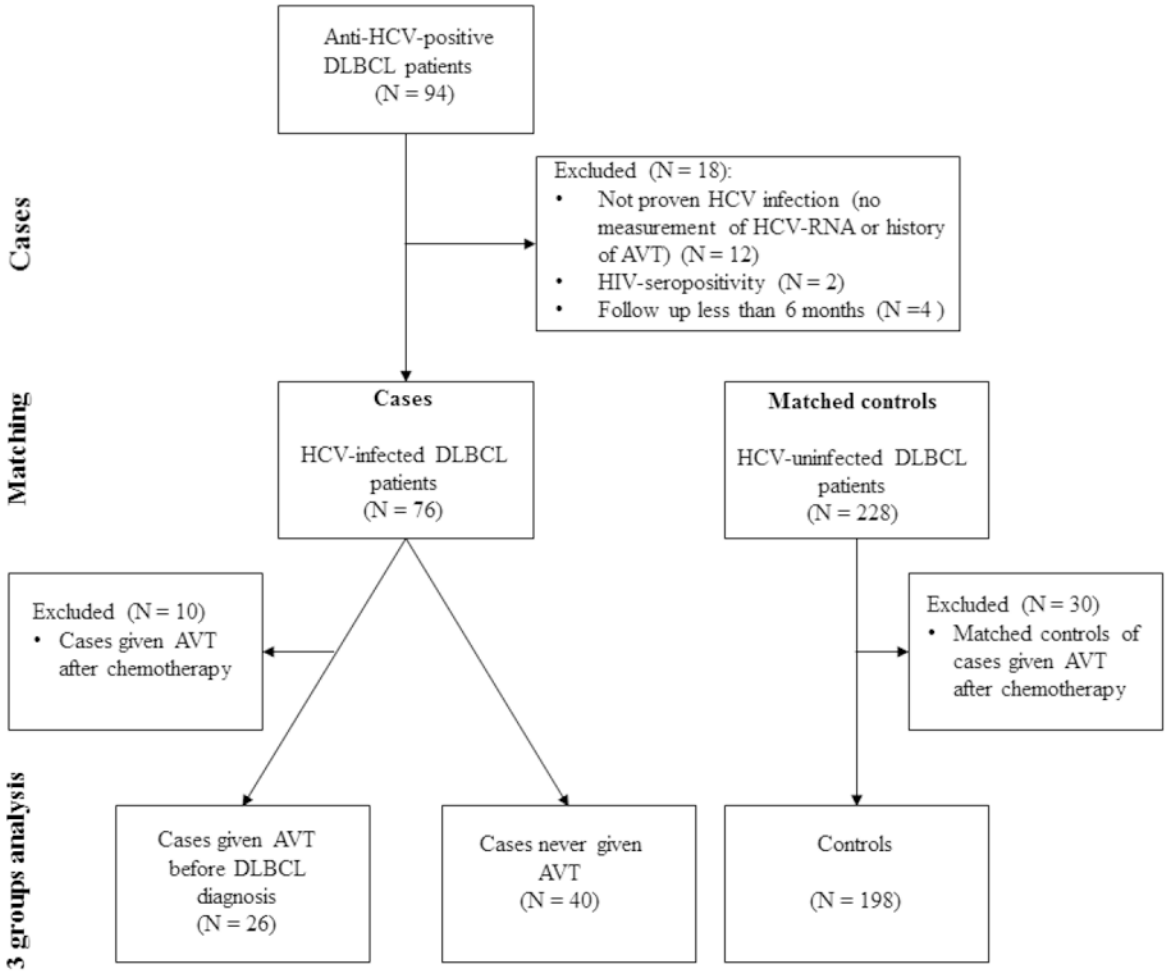

Figure 1. Flow diagram

AVT indicates antiviral therapy; CT, chemotherapy; DLBCL, diffuse large B-cell lymphoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

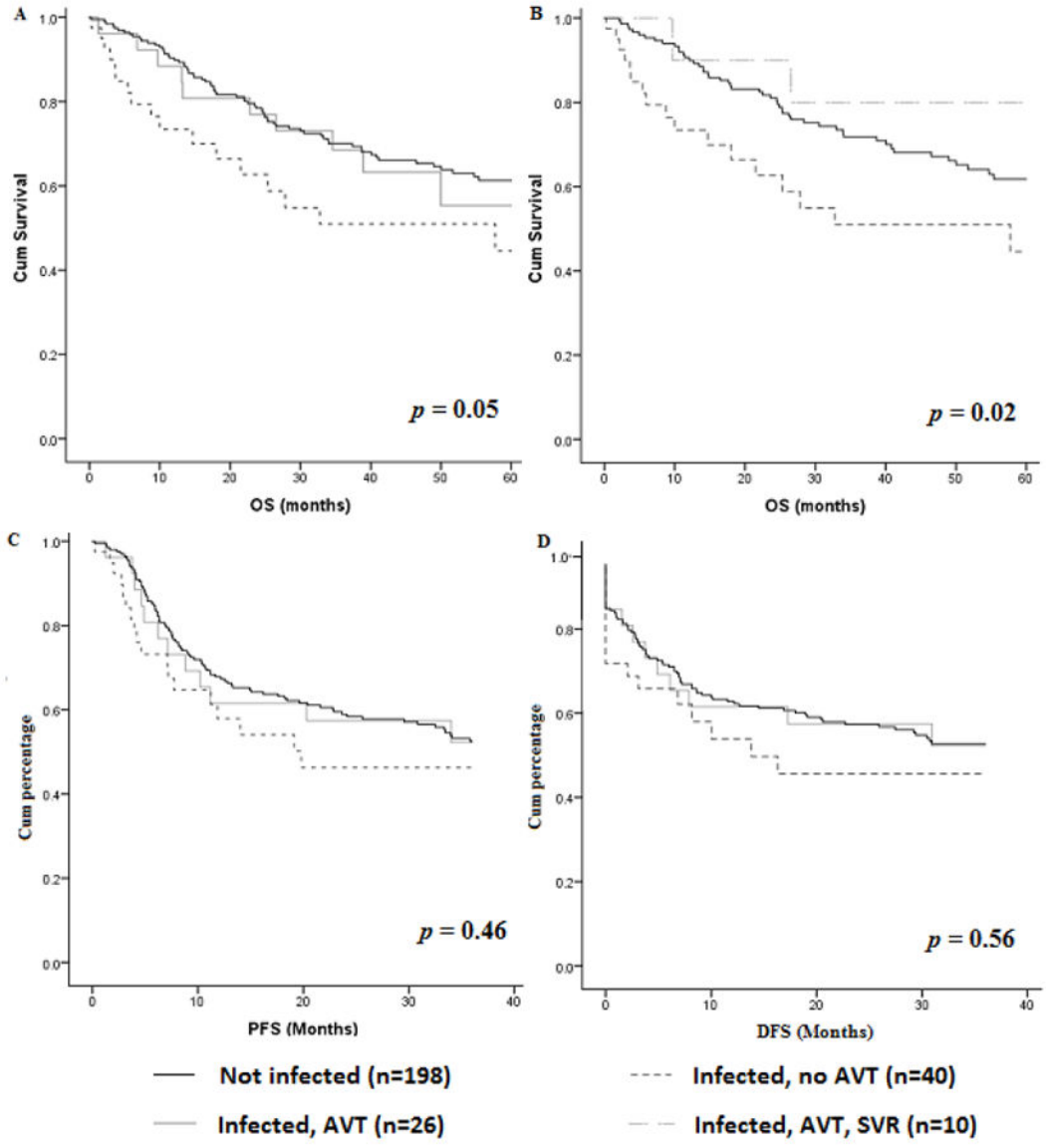

Figure 2. Comparison of the 5-year OS, 3-year PFS and DFS rates in the uninfected controls, HCV-infected cases never given AVT, and HCV-infected cases given AVT before DLBCL diagnosis

(A) Five-year OS rate. (B) Five-year OS rate including only patients achieving SVR. (C) Three-year PFS rate. (D) Three-year DFS rate.

AVT indicates antiviral therapy; DFS, disease free survival; HCV, hepatitis C virus; PFS, progression free survival; OS, overall survival; SVR, sustained virologic response.

Table 1

Demographics, DLBCL Characteristics, and Oncologic Treatment in the HCV-Infected Cases and Uninfected Controls

Characteristic	Cases (N=76) No. of Patients (%)	Controls (N=228) No. of Patients (%)	*p*
Age, years [median (IQR)]	59 (53-63)	59 (53-64)	Matched
Sex	N = 76	N = 228	Matched
Male	53 (70)	159 (70)	
Female	23 (30)	69 (30)	
Race	N = 75	N = 225	0.01
White	51 (68)	175 (78)	
Black	14 (19)	9 (4)	
Hispanic	6 (8)	33 (15)	
Other *	4 (5)	8 (3)	
Transformation of DLBCL	N = 76	N = 228	0.28
De novo DLBCL	55 (72)	178 (78)	
Transformed DLBCL †	21 (28)	50 (22)	
DLBCL subtype	N = 54	N = 198	0.39
GCB	30 (56)	123 (62)	
Non-GCB	24 (44)	75 (38)	
Ann Arbor stage	N = 75	N = 228	Matched
1-2	15 (20)	45 (20)	
3-4	60 (80)	183 (80)	
ECOG score	N = 62	N = 207	0.13
0-1	44 (71)	165 (80)	
2-4	18 (29)	42 (20)	
IPI score	N = 58	N = 205	0.37
Low risk (0-1)	21(36)	63 (31)	
Intermediate risk (2-3)	24 (41)	106 (51)	
High risk (4-5)	13 (23)	36 (18)	
Presence of B symptoms	24/73 (33)	82/219 (38)	0.47
Extra nodal involvement	60/76 (79)	164/228 (72)	0.07
Upper GI ‡ and splenic involvement	32/76 (42)	54/228 (24)	0.004
Para-aortic lymph node involvement	44/76 (58)	110/218 (50)	0.24
Bone marrow involvement	27/74 (36)	61/228 (27)	0.08
Cirrhosis at DLBCL diagnosis	18/76 (24)	4/220 (2)	<0.0001
First-line CT	N = 75	N = 228	0.91
R-CHOP	54 (72)	165 (72)	
Other §	21 (28)	63 (28)	
Second-line CT	N = 33	N = 105	0.55
R-ICE	19 (58)	64 (61)	
Other ‖	14 (42)	41 (39)	

Characteristic	Cases (N=76) No. of Patients (%)	Controls (N=228) No. of Patients (%)	*p*
Radiotherapy	18/74 (24)	62/228 (27)	0.55
HCT	16/74 (22)	66/228 (29)	0.15
Mortality/survival	N = 76	N = 228	0.79
Dead	30 (39)	94 (41)	
Cause of death	N = 26	N = 71	--
Refractory DLBCL	15 (58)	45 (63)	
Liver failure	2 (8) ¶	0	
Infections other than HCV	4 (15)	9 (13)	
Others#	5 (19)	17 (24)	

DLBCL indicates diffuse large B-cell lymphoma; GCB, germinal center B-cell; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; GI, gastrointestinal; CT, chemotherapy; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone; R-ICE, rituximab-ifosfamide, carboplatin, and etoposide; HCT, hematopoietic stem cell transplantation; HCV, hepatitis C virus.

*Asian or Pacific Islander.

†According to composite or discordant biopsy results (lymph node and bone marrow biopsies) or a previous history of indolent lymphoma.

‡Stomach, liver, and/or pancreas.

§Rituximab-etoposide, prednisone, Oncovin (vincristine), cyclophosphamide, and hydroxydaunorubicin (doxorubicin) (R-EPOCH); rituximab-cyclophosphamide, vincristine, doxorubicin (Adriamycin), and dexamethasone (R-hyper-CVAD); or CHOP. Only three patients did not receive rituximab.

‖Rituximab-etoposide, methylprednisolone, cytarabine, and cisplatin (R-ESHAP); rituximab-gemcitabine and oxaliplatin (R-GEMOX); rituximab-dexamethasone, cytarabine, and cisplatin (R-DHAP); or rituximab-mesna, ifosfamide, novantrone, and etoposide (R-MINE).

¶Bulky disease at the level of hepatic hilum (n=1), septic shock with multiorgan failure (n=1).

#Myocardial infarction, tamponade, or other cancers.

Table 2

Response to CT and Relapse Rates in the Three DLBCL Patient Groups

Variable	No. of Patients (%)			*p*		
	Cases Given AVT (A)	Cases Never Given AVT (B)	Controls (C)	All Three Groups*	(A *v* B)†	(B *v* C)*
Response to first-line CT‡	N = 26	N = 36	N = 198	0.15	0.11	0.05
CR or PR	22 (85)	24 (67)	165 (83)			
Progressive disease	4 (15)	12 (33)	33 (17)			
Relapse after first CR, PR‡	N = 22	N = 24	N = 163	0.88	0.73	0.66
Yes	9 (41)	11 (46)	66 (40)			
No	13 (59)	13 (54)	97 (60)			
Oncologic outcome at last follow-up‡	N = 26	N = 36	N = 197	0.18	0.06	0.09
CR or PR	19 (73)	18 (50)	135 (69)			
Progressive disease	7 (27)	18 (50)	62 (31)			

AVT indicates antiviral therapy; CT, chemotherapy; CR, complete response; and PR, partial response.

*Generalized estimating equations and logit link function.

†Pearson chi-square test.

‡Ten patients who received AVT after CT were not included.

Table 3

Comparison of Cases Given AVT and Cases Never Given AVT.

	Cases given AVT No. of patients (%)	Cases never given No. of patients (%)	*p*
Total number of patients	N=26	N=40	
Demographics			
Age, years [median (IQR)]	58 (54 - 65)	59 (53 - 63)	0.89
Gender, male	21/26 (81)	26/40 (65)	0.16
Race, white	19/26 (73)	25/39 (64)	0.44
DLBCL characteristics			
De novo DLBCL	21/26 (81)	28/40 (70)	0.32
Immunohistochemistry, GCB	11/19 (58)	16/29 (55)	0.85
Ann Arbor, stage 3-4	19/25 (76)	33/40 (83)	0.52
Extranodal involvement	20/26 (77)	31/40 (78)	0.95
Presence of B symptoms	8/26 (31)	12/37 (32)	0.88
ECOG score, 2-4	7/23 (30)	10/32 (31)	0.94
IPI score, high risk	7/19 (37)	5/31 (16)	0.17
Bone marrow biopsy, positive	8/26 (31)	15/38 (40)	0.47
LDH level, U/L [median (IQR)]	631 (522 - 943)	657 (499 - 1075)	0.66
Infectious characteristics			
HCV genotype 1	13/21 (62)	27/34 (79)	0.15
HbsAg, positive	0	2/40 (3)	0.51
HbcAb, positive	12/26 (46)	18/40 (45)	0.92
HBV DNA, detected	2/10 (20)	2/17 (12)	0.61
Hepatic characteristics			
Cirrhosis	5/26 (19)	10/40 (25)	0.58
Child Pugh score A	3/5 (60)	4/10 (40)	0.61
Portal hypertension	4/5 (80)	9/10 (90)	0.90
METAVIR, stage 3-4	9/16 (56)	2/10 (20)	0.10
Oncologic treatment			
First line chemotherapy, RCHOP	20/26 (77)	25/29 (86)	0.27
HCT	6/26 (23)	7/38 (18)	0.64
Radiotherapy	8/26 (31)	11/38 (29)	0.87
Received further chemotherapy	12/26 (46)	16/37 (43)	0.81
Second line chemotherapy, RICE	8/13 (62)	10/15 (67)	>0.99
Oncologic outcomes			
PFS, months [median (IQR)]	27 (7 - 45)	10 (4 - 42)	0.18
DFS, months [median (IQR)]	24 (3 - 41)	6 (0 - 34)	0.10
OS, months [median (IQR)]	39 (26 - 56)	16 (6 - 41)	0.02

AVT indicates antiviral therapy; IQR, interquartile range; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; HCV, hepatitis C virus; HbsAg, hepatitis b surface antigen; HbcAb, hepatitis b core antibody; HBV, hepatitis B virus; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone; HCT, hematopoietic stem cell transplantation; R-ICE, rituximab-ifosfamide, carboplatin, and etoposide; PFS, progression free survival; DFS, disease free survival; and OS, overall survival.

Table 4

Multivariable cox regression analyses

	Controls (N = 120) *v* Cases Never Given AVT (N = 40)*			Cases Given AVT (N = 26) *v* Cases Never Given AVT (N = 40)†		
Parameter	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
HCV (infected without AVT *v* uninfected)	2.31	1.01 -5.30	0.04	--	--	--
Race (white *v* non-white)	1.20	0.52 – 2.76	0.65	--	--	--
Immunohistochemistry (GCB *v* non- GCB)	1.6	0.78 – 3.41	0.18	--	--	--
IPI score (moderate *v* low risk)	2.42	0.96 – 6.09	0.05	1.45	0.47 – 4.34	0.50
IPI score (high *v* low risk)	4.66	1.47 – 14.79	0.008	2.68	0.7 – 9.7	0.13
Cirrhosis (yes *v* no)	5.66	1.82 – 17.60	0.002	11.56	3.92 - 34.04	<0.001
AVT (yes *v* no)	--	--	--	0.21	0.06 - 0.69	0.01

AVT indicates antiviral therapy; HCV, hepatitis C virus; GCB, germinal center B-cell; and IPI, International Prognostic Index

*Model analyzing the effect of active HCV infection on 5-year mortality rate after adjustment for race, immunohistochemistry, cirrhosis and IPI score (based on age, Ann Arbor stage, ECOG score, number of involved extranodal sites and LDH that are the oncologic prognostic factors of DLBCL).

†Model analyzing the effect of AVT on 5-year mortality rate after adjustment for cirrhosis and IPI score (based on age, Ann Arbor stage, ECOG score, number of involved extranodal sites and LDH that are the oncologic prognostic factors of DLBCL).

Note: Confounders that changed the estimate by ≥ 10% or are clinically significant were selected. The proportional hazards assumption was tested with Schoenfeld residuals and by introducing an interaction term between the covariate and the follow-up time in the model.