Clinical outcome in diffuse large B-cell lymphoma with hepatitis C virus infection in the rituximab era: A single center experience

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Abstract. Clinical outcome of diffuse large B-cell lymphoma (DLBCL) patients with hepatitis C virus (HCV) infection in the rituximab era remains unclear. The aim of the present study was to compare the clinical outcome, treatment response and hepatotoxicity in DLBCL patients who received rituximab containing immunochemotherapy that had HCV infection and those that did not have HCV infection between January 2004 and October 2011. Of the 272 consecutive histopathologically diagnosed DLBCL patients in our department, a total of 248 were retrospectively analyzed in the present study. There were 28 DLBCL patients with HCV infection (the HCV group) and 220 DLBCL patients without HCV infection (the control group). We compared overall survival (OS), progression-free survival (PFS), treatment response and hepatotoxicity according to HCV infection. In terms of OS (P=0.525) and PFS (P=0.759), there were no significant differences between the HCV group and the control group. Objective response rates were 92.9% (26/28) in the HCV group and 95.9% (211/220) in the control group (P=0.619). In the HCV group, seven patients (25.0%) developed hepatotoxicity during immunochemotherapy. In the control group, 35 patients (15.9%) developed hepatotoxicity during chemotherapy. No patient required discontinuation of immunochemotherapy owing to hepatotoxicity in either group. In terms of hepatotoxicity, there was no significant difference between these two groups (P=0.281). In conclusion, our study results suggested that HCV infection might not influence the clinical course in DLBCL patients who receive rituximab-containing immunochemotherapy.

Introduction

A number of epidemiologic studies have demonstrated an association between non-Hodgkin's lymphoma (NHL) and hepatitis C virus (HCV) infection, suggesting that HCV plays a role in the development of NHL (1-8). Low-grade marginal zone lymphoma has been the lymphoma subtype most commonly associated with HCV-infection, while limited data are available regarding HCV-positive patients with diffuse large B-cell lymphoma (DLBCL) (9). Clinicopathological characteristics at presentation, tolerance to chemotherapy, natural history and clinical outcome of patients with HCV-positive DLBCL are still unclear. This is due to the heterogeneity in histology and treatment strategies for DLBCL with HCV infection and a lack of data based on large series of unselected patients (2). Previous studies involving lymphoma patients with HCV infection have shown good tolerance to standard chemotherapy (i.e., cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimens) (10,11). However, these studies were mainly conducted before the use of rituximab in DLBCL patients. On the other hand, there are several reports that DLBCL patients with HCV infection may exhibit a characteristic clinical presentation, poor tolerance to intensive chemotherapy and poorer survival (12,13).

Rituximab, a human/mouse chimeric monoclonal antibody that reacts specifically with the CD20 antigen, was approved for use in DLBCL patients in 2002 in Japan. Since its introduction, rituximab has been widely used for the treatment of DLBCL regardless of patient age (2,14). In general, its associated toxicity is usually mild and limited to the infusion period (14). In DLBCL patients with HCV infection, rituximab has been reported to increase alanine aminotransferase (ALT) levels and HCV viral load (15). However, the prognostic value of HCV infection in rituximab combination chemotherapy has not been well established. To our knowledge there have been few reports describing the clinical outcome in DLBCL patients with HCV infection who received rituximab containing immunochemotherapy, although hepatitis B virus (HBV) reactivation is a well-documented complication that often develops after performing rituximab containing immunochemotherapy in DLBCL patients, and has proved fatal in some cases (9,16-19).

The aim of the present study was to compare clinical outcome, treatment response and hepatotoxicity in patients with DLBCL who received rituximab containing immunochemotherapy that had HCV infection and those that did not have HCV infection.

Patients and methods

Patients. The subjects consisted of 272 consecutive histopathologically proven DLBCL patients admitted to the Department of

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Hematology, Osaka Red Cross Hospital, Japan between January 2004 and October 2011. DLBCL was diagnosed by an expert hematopathologist in our hospital, based on the World Health Organization classification (20). Of these 272 patients, 2 patients who did not undergo rituximab containing immunochemotherapy, one patient whose serum human immunodeficiency virus (HIV) antibody was positive, 13 patients whose serum hepatitis B antigen was positive, and 8 patients who had been lost to follow-up were excluded from the present study (Fig. 1). A total of 248 DLBCL patients were analyzed. All of them had undergone rituximab containing immunochemotherapy and had no malignancies other than DLBCL at the time of DLBCL diagnosis. There were 28 DLBCL patients with HCV infection (the HCV group) and 220 DLBCL patients without HCV infection (the control group) in the present study. HCV infection was defined as the detection of anti-HCV antibodies with commercially available second- or third-generation immunoassay kits (Monolisa anti-HCV Plus, Sanofi Diagnostics Pasteur; and Axsym HCV Version 3.0, Abbott Laboratories). Of the 28 DLBCL patients with HCV infection, none received interferon (IFN) therapy for hepatitis C during the follow-up period. Before performing rituximab containing immunochemotherapy, written informed consent was obtained from all patients. This retrospective study protocol complied with all of the provisions of the Declaration of Helsinki.

Virological study. All patients analyzed in the present study were tested for the presence of serum antibodies against HCV, before the initiation of immunochemotherapy for DLBCL. HCV genotype was determined using the polymerase chain reaction (PCR) amplification of the core region of the HCV genome by means of genotype-specific PCR primers (21). Serum HCV-RNA levels were quantified using the COBAS Amplicor HCV Monitor test, version 2.0 (detection range 6-5000 KIU/ml: Roche Diagnostics, Branchburg, NJ, USA). Serum HBV antigen, as well as HIV antibodies, were also tested on all patients analyzed in the present study using commercial enzyme immunoassays at the time of lymphoma diagnosis.

Clinical staging. All records registered in our database were retrospectively reviewed to verify clinical outcome, clinical staging, presentation and treatment. Clinical staging evaluation included routine laboratory tests, physical examination, bone marrow aspirate and biopsy, chest radiographs and computed tomography (CT) of the chest and whole abdomen. CT of the neck, an abdominal ultrasonographic study, esophagogastroduodenoscopy, colonoscopy, spleen biopsy and liver biopsy were performed when clinically indicated. All patients were classified according to the Ann Arbor staging system (22).

Treatment and response. In the present study, R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) had been performed in patients aged <65 years. R-THP-COP therapy (rituximab, therarubicin, cyclophosphamide, vincristine and prednisone) had been performed in patients aged ≥65 years. The initial chemotherapy dose was determined mainly based on the decisions of the attending physicians, considering factors such as laboratory data, general condition and underlying diseases. Sensitivity to chemotherapy was evaluated in each patient using CT and positron emission tomography (PET)/CT with ^{18}F-fluorodeoxyglucose imaging (23). Complete remission (CR) was defined as the absence of disease for ≥1 month after the end of immunochemotherapy. Partial response (PR) was defined as >50% reduction in tumor area measurable in two dimensions. Progressive disease (PD) was defined as enlargement of disease or the development of disease in a previously involved site. Relapse was defined as the occurrence of disease progression ≤1 month after CR or PR.

Liver function tests and assessment of liver toxicity. In all patients analyzed in the present study, pretreatment levels of ALT and its highest levels during immunochemotherapy were collected for analysis. Definition and grading of hepatic toxicity relied on the standard National Cancer Institute-World Health Organization (NCI-WHO) common toxicity criteria grading scale. In patients with normal ALT at baseline, significant liver toxicity was defined as a WHO toxicity of grade ≥2 (≥2.5xULN), and in patients with abnormal ALT values at baseline, significant liver toxicity was defined as ≥3.5 times elevation of ALT relative to the baseline value (24). Liver function tests were monitored carefully before and during immunochemotherapy, as well as during the follow-up period.

Follow-up. All patients were followed up every 3 months with laboratory tests, CT scans and/or PET/CT after the completion of immunochemotherapy. When lymphoma relapse was detected using imaging modalities and/or laboratory tests, additional chemotherapy was performed after histopathological examination.

Statistical analysis. The primary end-point was OS and the secondary end-point was PFS. Differences between the two groups were analyzed using the unpaired t-test for continuous variables, and the categorical variables were analyzed using the χ^2 test or continuity correction method. The overall survival (OS) curves and the progression-free survival (PFS) curves were generated using the Kaplan-Meier method and compared using the log-rank test. OS was calculated from the treatment initiation date until death from any cause or the last follow-up. PFS was calculated from the treatment initiation date to the date of documented disease progression, relapse or the end date of the study. All statistical tests were two-sided. All data were analyzed using SPSS software, version 9.0 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows. Data are expressed as means ± standard deviation. $P<0.05$ was considered statistically significant.

Results

Baseline characteristics. The baseline characteristics of the patients enrolled in the present study are shown in Table I. There were significant differences in age (P=0.030), platelet count (P=0.001) and white blood cell count (P=0.017) between the HCV group and the control group. The proportion of patients that had a high and high-intermediate International prognostic index (IPI) (25) was almost the same between the two groups (P=1.000). There were 157 out of the 248 (63.3%) DLBCL patients with primary extranodal disease. The stomach was the most frequently involved extranodal organ (44 out of 248, 17.7%), followed by the small intestine (19 out of 248, 7.7%) and the spleen (16 out of 248, 6.5%).

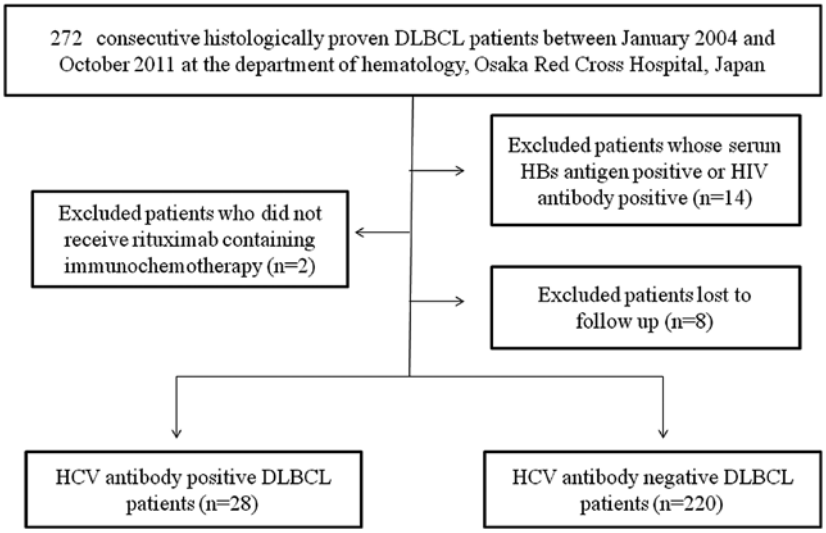

Figure 1. Study profile.

Table I. Baseline characteristics between the HCV group and the control group.

	HCV group (n=28)	Control group (n=220)	P-value
Age (years)	72.1±7.8	66.5±13.2	0.030[a]
Gender (male/female)	15/13	113 / 107	0.844[b]
DLBCL stage			
I	8	39	0.900[b]
II	11	79	
III	5	42	
IV	6	60	
IPI (H or HI/L or LI)	12/16	97 / 123	1.000[a]
White blood cells (cells/mm^3)	5603.6±2297.9	6900.3±2732.5	0.017[a]
Hemoglobin (g/dl)	12.6±1.8	12.2±2.2	0.363[a]
Platelets (x10^4/mm^3)	16.8±7.3	23.0±9.0	0.001[a]
AST (IU/l)	46.3±32.9	45.1±179.6	0.972[a]
ALT (IU/l)	35.6±33.1	33.4±152.2	0.938[a]
Total bilirubin (mg/dl)	0.82±0.39	0.75±0.63	0.574[a]
Albumin (g/dl)	3.84±0.42	3.84±0.63	0.995[a]
Prothrombin time (%)	92.5±10.2	96.0±17.3	0.308[a]
LDH (IU/l)	350.5±283.2	478.3±949.1	0.480[a]
sIL2R (U/ml)	2653.1±3974.5	3389.0±5448.1	0.490[a]
Creatinine (mg/dl)	0.90±0.34	0.94±0.57	0.653[a]
Body mass index (kg/m^2)	22.4±2.1	21.8±3.4	0.393[a]
Diabetes mellitus (yes/no)	11/17	56/164	0.173[a]

HCV, hepatitis C virus; DLBCL, diffuse large B cell lymphoma; IPI, international prognostic index; H or HI, high or high-intermediate; L or LI, low or low-intermediate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; sIL2R, soluble interleukin 2 receptor; [a]unpaired t-test; [b]χ^2 test or continuity correction method.

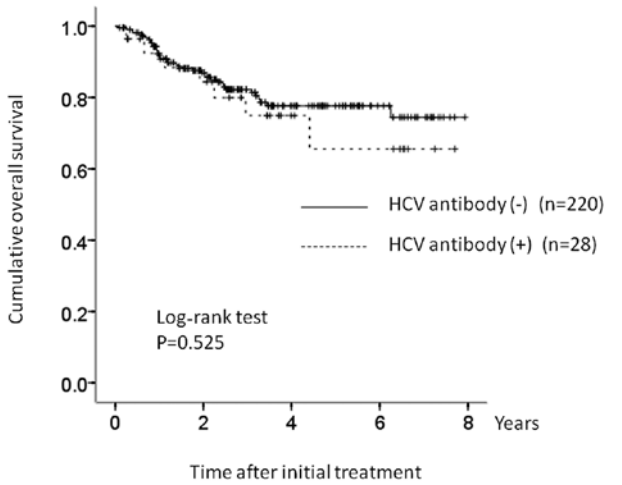

Figure 2. Cumulative overall survival in the HCV and control groups. The 1-, 3- and 5-year overall survival rates were 90.2, 75.5 and 66.3%, respectively, in the HCV group and 90.3, 81.2 and 77.5%, respectively, in the control group. In terms of overall survival, there was no significant difference between these two groups (P=0.525).

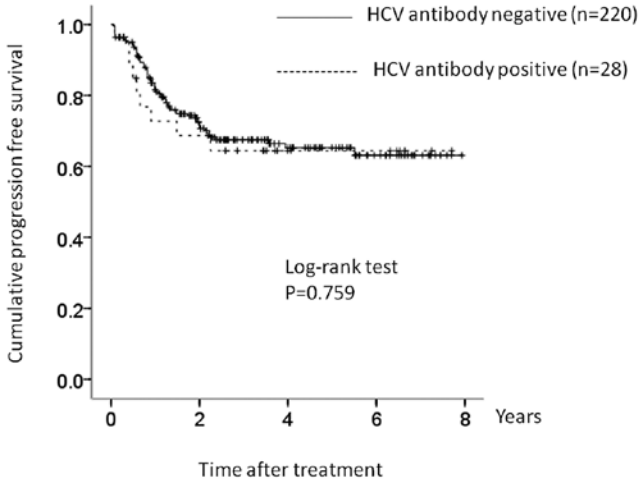

Figure 3. Cumulative progression-free survival in the HCV and control groups. The progression-free survival rates at 1, 3 and 5 years were 74.4, 63.8 and 63.8%, respectively, in the HCV group and 80.7, 67.0 and 65.1%, respectively, in the control group. In terms of progression-free survival, there was no significant difference between these two groups (P=0.759).

HCV genotype and viral load. In 18 patients tested, HCV genotype was detected in genotype 1 in 17 patients and genotype 2 in 1 patient, respectively. In 18 patients who were tested for HCV viral load, 17 patients had a high viral load (≥100 kIU/ml) and one patient had a low viral load (<100 kIU/ml), according to Japanese criteria.

Overall survival. The median follow-up period was 3.4 years (0.3-7.7 years) in the HCV group and 2.6 years (0.2-7.9 years) in the control group. Seven patients (25.0%) in the HCV group died during the follow-up period. The causes of death in the HCV group were HCC (4 patients), progression of malignant lymphoma (2 patients) and miscellaneous (1 patient). Thirty-five patients (15.9%) in the control group died during the follow-up period. The causes of death in the control group were progression of malignant lymphoma (33 patients), pancreatic cancer (1 patient) and lung cancer (1 patient).

The 1-, 3- and 5-year OS rates were 90.2, 75.5 and 66.3%, respectively, in the HCV group and 90.3, 81.2 and 77.5%, respectively, in the control group (Fig. 2). The corresponding PFS rates at 1, 3 and 5 years were 74.4, 63.8 and 63.8%, respectively, in the HCV group and 80.7, 67.0 and 65.1%, respectively, in the control group (Fig. 3). In terms of OS (P=0.525) and PFS (P=0.759), there were no significant differences between the two groups.

Treatment response. In the HCV group, a CR was obtained in 24 patients (85.7%) and a PR was obtained in 2 patients (7.1%) after the front-line therapy. The objective response rate (ORR) in the HCV group was 92.9% (26/28). In the control group, a CR was obtained in 204 patients (92.7%) and a PR was obtained in 7 patients (3.2%) after the front-line therapy. The ORR in the control group was 95.9% (211/220). In terms of ORR, there was no significant difference between the two groups (P=0.619).

Liver dysfunction. As shown in Table I, the pretreatment transaminase levels were not significantly different between the two groups. In the HCV group, 7 patients (25.0%) developed hepatotoxicity during immunochemotherapy. In the HCV group, immunochemotherapy was not discontinued in any of the patients owing to hepatotoxicity. In the control group, 35 patients (15.9%) developed hepatotoxicity during chemotherapy, and none of the patients had immunochemotherapy discontinued owing to hepatotoxicity. In terms of hepatotoxicity, there was no significant difference between the two groups (P=0.281).

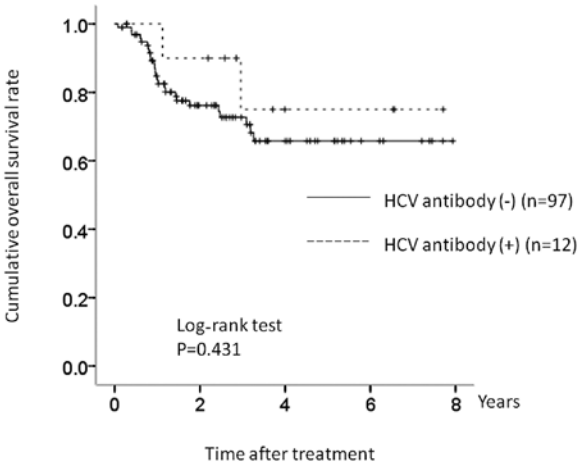

Figure 4. Cumulative overall survival in patients with high or high-intermediate IPI values. There were 12 patients in the HCV group and 97 patients in the control group. In terms of overall survival, there was no significant difference between these two groups (P=0.431).

Subgroup analysis according to IPI: high or high/intermediate IPI group. There were 12 patients (42.9%) with high or high/intermediate IPI values in the HCV group, and 97 patients (44.1%) with high or high/intermediate IPI values in the control group. In terms of OS, there was no significant difference between the two groups (P=0.431) (Fig. 4).

Subgroup analysis according to IPI: low or low/intermediate IPI group. There were 16 patients (57.1%) with low or low/inter-

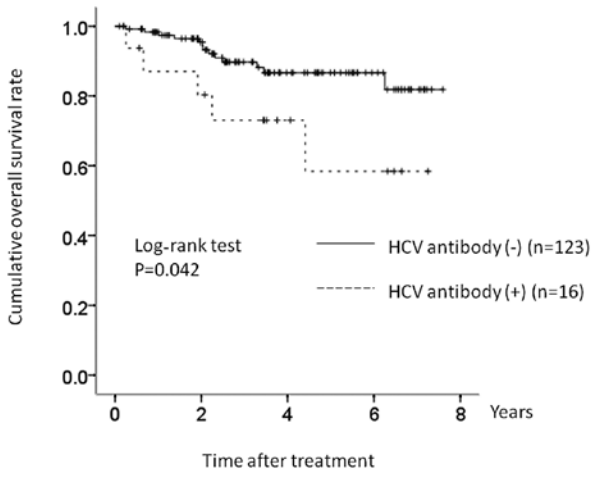

Figure 5. Cumulative overall survival in patients with low or low-intermediate IPI values. There were 16 patients in the HCV group and 123 patients in the control group. In terms of overall survival, there was a significant difference between these two groups (P=0.042).

mediate IPI values in the HCV group, and 123 patients (55.9%) with low or low/intermediate IPI values in the control group. In terms of OS, there was a significant difference between these two groups (P=0.042) (Fig. 5).

Discussion

Over the past two decades, considerable evidence has accumulated with regard to the association between HCV and several hematologic malignancies, most notably B-cell NHL (9). However, there have been few reports regarding the clinical outcome of DLBCL in patients with HCV infection who have undergone rituximab containing immunochemotherapy (2,12).

In the present study, 28 patients (10.3%) out of the 272 DLBCL patients were anti-HCV-positive. The prevalence of HCV is reported to be higher in patients with B-NHL (~15%) than in the general population (1~2%), particularly in geographical areas with a high incidence of HCV infection (8-10). Our results were similar to those reported in previous studies.

In terms of OS and PFS, there were no significant differences between the HCV group and the control group in the present study. Our results suggested that in DLBCL patients, HCV infection was not a significant risk factor for prognosis in rituximab containing immunochemotherapy.

In the present study, favorable objective response to immunochemotherapy was obtained in the HCV group as compared with previous reports (2,12,26), and there was no significant difference between the HCV group and the control group in terms of ORR. Besson *et al* reported that the CR rate of DLBCL patients with HCV infection did not differ from control patients (12); our results were similar and suggested that the addition of rituximab did not seem to affect the treatment response of DLBCL patients with HCV infection.

Although the addition of rituximab to the chemotherapy regime for ML patients heralded a new treatment era, hepatotoxicity due to immunochemotherapy is an important consideration. Besson *et al* (12) reported that the hepatotoxicity of HCV-positive ML patients undergoing chemotherapy could not be attributed to pretreatment liver abnormalities or to a specific drug, whereas Ennishi *et al* (2) reported that hepatotoxicity in HCV-positive ML patients undergoing chemotherapy was more likely to occur if pretreatment transaminase levels were high. In the present study, in the HCV group, three patients out of five (60.0%) with high pretreatment transaminase levels developed hepatotoxicity during immunochemotherapy, whereas in the control group only one patient out of twenty (5.0%) with high pretreatment transaminase levels developed hepatotoxicity during immunochemotherapy. Our results are similar to those reported by Ennishi *et al* (2) and indicate that careful monitoring of liver function during immunochemotherapy will be required, especially in HCV-positive DLBCL patients with high pretreatment transaminase levels.

In our study, there were no patients in the HCV group who required discontinuation of immunochemotherapy owing to hepatotoxicity or other causes. These results suggest that rituximab containing immunochemotherapy is safe in DLBCL patients with HCV infection, although Arcaini *et al* reported that a significant proportion of patients with HCV-positive NHL developed liver toxicity (13). This often led to interruption or discontinuation of treatment, and was a limiting factor in the application of immunochemotherapy programs (13).

In the present study, in terms of OS, there was a significant difference in the low/low intermediate IPI group, although there was no significant difference in the high/high intermediate IPI group. Our results suggested that the survival of DLBCL patients with favorable prognostic value may be more affected by HCV infection than those with poor prognostic value.

In the present study, four patients in the HCV group died of HCC, and all of them achieved a CR after the front-line therapy. Significant immunosuppression may change the tempo of HCV natural history and accelerate complications such as liver cirrhosis and HCC. In these patients, IFN therapy may be required with the objective of HCV eradication and suppression of HCC occurrence (27,28). La Mura *et al* reported that after complete response to chemotherapy, antiviral treatment in HCV-positive NHL might be an important strategy (29). Collaboration between hematologists and hepatologists is essential to optimize outcome.

Interestingly, out of 18 patients tested for HCV genotype in the present study, 17 (94.4%) had HCV genotype 1. Pellicelli *et al* reported that DLBCL patients with HCV infection had a higher prevalence of HCV genotype 1 as compared with patients with indolent B-NHL, in which HCV genotype 2 was the more frequent genotype (30); our results were similar to their report, although the reasons for this are unclear.

The present study had several limitations. First, it was a retrospective study. Second, the sample sizes between the HCV group and the control group were not balanced. Third, the cause of hepatotoxicity during immunochemotherapy in the HCV group was unclear, because drug induced liver injury or HCV reactivation since HCV-RNA was not tested during chemotherapy in many patients in the HCV group. Therefore, to clarify these issues, larger prospective studies will be needed in the future. However, it was confirmed in the present study that in both the HCV and control groups patients could achieve favorable clinical outcome, and in the HCV group they had good tolerance to immunochemotherapy. In conclusion, HCV infection may not influence the clinical course in DLBCL patients who received rituximab containing immunochemotherapy.

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