



Incidence of lymphoma in HIV-HCV-infected patients. Modifications in function of the anti-hepatitis C virus therapy

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Abstract

The change in the incidence of lymphomas in function of the presence or absence of sustained virological response after anti-hepatitis C therapy in a cohort of human immunodeficiency (HIV)-hepatitis C (HCV) viruses coinfecting patients was analyzed. A prospective cohort of 755 HIV-HCV coinfecting patients who received their first anti-HCV therapy, based on interferon + ribavirin schemas, was evaluated. Incidence and histologic types of lymphomas were analyzed in two periods: (1) before administration of anti-HCV therapy and (2) after anti-HCV therapy. The association between lymphoma incidence and demographic, HIV- (minimum CD4+ cell count and CD4+ cell count at diagnosis of lymphoma, antiretroviral therapy, maximal HIV load and HIV load at diagnosis of lymphoma) and HCV-related variables (HCV load, genotype, sustained viral response to anti-HCV therapy) were analyzed. A total of 13 lymphomas [incidence rate (95% confidence interval), 0.72 (0.33–1.11) × 1000 person-years, time from HIV diagnosis to lymphoma diagnosis (median, interquartile range), 15 (11–19) years] were diagnosed. Nine of them were non-Hodgkin and four Hodgkin lymphomas. The median CD4+ T cell count at diagnosis of lymphoma was 457/mm³, with only two cases with values lower than 200/mm³. The incidence rate of non-Hodgkin lymphomas was similar pre- and post-anti HCV therapy [0.33 (0.00–0.65) vs 0.68 (0.08–1.26) × 1000 person-years, respectively, $p > 0.05$]. Patients with sustained virologic HCV response showed similar incidence rate of lymphomas than that of those without anti-HCV response. In conclusion, anti-HCV therapy does not modify the incidence rate of lymphomas in HIV-HCV coinfecting patients.

Keywords HIV · Hepatitis C virus · Non-Hodgkin lymphoma · Hodgkin lymphoma · Interferon alpha · Ribavirin

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Introduction

Human immunodeficiency virus (HIV) infection has been associated with an increased risk of developing lymphoproliferative disorders [1]. Antiretroviral treatment (ART) has modified the course of HIV infection, including a decrease in the incidence of lymphomas and a change in the histologic characteristics of them [2, 3]. The incidence of non-Hodgkin lymphomas (NHL) associated with the immune depression, such as diffuse large B cell lymphoma (DLBCL) and its variant primary brain lymphoma (PBL) has decreased, and the incidence of those not associated with the immunodeficiency, such as Hodgkin (HL) and Burkitt (BL) lymphomas, has increased [2, 3].

Chronic hepatitis C virus (HCV) infection has been also associated to an increased incidence of lymphomas, mainly DLBCL, lymphoplasmocytic, and marginal zone lymphomas [4–6]. T cell, follicular, and Hodgkin's lymphomas have not

been consistently linked to HCV infection [4–6]. Regression of marginal zone lymphomas in HCV-infected individuals after anti-HCV therapy has been observed [7]. Furthermore, treatment of HCV infection decreases the overall incidence of lymphomas in HCV monoinfected patients [8].

The influence of HCV on lymphoma incidence rate in HIV-HCV coinfecting patients is controversial. Several authors have communicated that HCV infection does not increase NHL risk among HIV-positive individuals [9–11]. In contrast, Wang et al. have detected that those patients with HIV-HCV coinfection show rates of NHL 5.4 times higher than those with HIV mono-infection [12].

The effects of anti-HCV therapy on the incidence and histologic type of lymphomas in a population of HIV-HCV coinfecting individuals have not been previously assessed. In the present work, we have analyzed a cohort of HIV-HCV coinfecting patients treated with anti-HCV drugs to evaluate the change in the incidence of lymphomas in function of the presence of sustained virological HCV response.

Patients and methods

Study population

From January 2001 to December 2013, a prospective cohort of 755 HIV-HCV coinfecting patients, older than 18 years, who received their first anti-HCV therapy was followed in 6 hospitals in Spain.

Inclusion criteria were:

1. Diagnosis of HIV and HCV coinfection
2. Treatment with interferon-alpha (IFN) plus ribavirin (RBV). Due to the limited follow-up of patients after direct-acting antivirals against HCV, patients who received these treatments were not included.
3. Evaluable response to anti-HCV therapy
4. Follow-up for at least 12 months after the end of anti-HCV treatment. Patients with hepatitis B virus infection (HbsAg positive) were excluded

Definitions and treatment schedule

Duration of HIV infection was estimated using an interviewer-assisted questionnaire assessing risk factors for HIV infection: the earliest exposure was designated as the time of acquisition [13]. The indication of starting ART changed during the study period; the final decision on starting ART and the specific drug combination was decided by the caring physician. Plasma HIV-RNA, identified by polymerase chain reaction (PCR) assay, lower than 50 copies/ml was considered as undetectable HIV load.

Positive serum antibodies against HCV and persistent (more than 6 months) HCV-RNA (quantitative PCR) were required for the diagnosis of chronic HCV infection. The HCV genotype was identified by line-probe assay. Diagnosis of chronic hepatitis or cirrhosis was established according to histological criteria when liver biopsy was performed or by transient elastography [14].

Patients were treated with peg-IFN α -2a (180 mg/week) or α -2b (1.5 mg/kg/week) subcutaneously plus oral RBV (800–1200 mg/day). Treatment duration was 48 weeks for carriers of HCV genotype 1 or 4. Patients bearing HCV genotype 2 or 3 received therapy during 24 weeks if they showed undetectable plasma HCV RNA load at week 4, and 48 weeks if otherwise. Sustained virological response (SVR) was defined as undetectable serum HCV RNA 24 weeks after completing treatment. Other virologic response, including non response, virologic breakthrough, relapse, or premature withdrawal due to adverse events or voluntary dropout, was considered virological failure.

The diagnosis of lymphoma was performed by biopsy study in all cases. Pathological materials were evaluated by expert hematopathologists from each hospital and classified according to the World Health Organization (WHO) classification [15]. Lymphoma staging and extranodal involvement was determined according to the Ann Arbor classification. The treatment of lymphoma was prescribed by the caring hematologist in charge of each patient. Complete response (CR) was considered as the lack of evidence of lymphoma at the end of treatment lasting for at least 1 month after the completion of chemotherapy. Any other situation (partial response, stable disease, or progression) was considered as therapeutic failure. Relapse was defined as the presence of lymphoma in a patient who had been in complete remission for a minimum of 2 months.

Study schedule

Patients were analyzed in two separate periods: (1) from the diagnosis of HIV infection to the end of anti-HCV therapy and (2) from the end of anti-HCV therapy until the date of lymphoma diagnosis, death, 6 months after the last visit, or the end of the study period. The date of study closure was December 2016.

Data collected included information about patient demographic, HIV-related (age at HIV infection, CDC stage, ART, HIV RNA viral load, and CD4 cell count at baseline and at diagnosis of lymphoma) and HCV-related (genotype, HCV load at the beginning of the HCV therapy, cirrhosis, SVR) characteristics, as well as lymphoma histologic type, extension, treatment, and survival. Time from HIV diagnosis to lymphoma diagnosis (time HIV-to-lymphoma) and time from end of HCV therapy to lymphoma diagnosis (time anti-HCV-to-lymphoma) were calculated.

Statistical analysis

The primary endpoint of the study was the incidence of lymphoma. The incidence was calculated as lymphoma rate (95% confidence interval) [LIR (95%CI)], expressed as person-years (PY), in the two previously indicated periods. Also, in the second period, incidence of lymphoma was analyzed in function of the presence or absence of SVR to HCV therapy. Additionally, we determined the association between lymphoma incidence and demographic, HIV- and HCV-related variables.

Continuous variables were expressed as median (interquartile range, IQR) and categorical variables as number (percentage). Continuous variables were compared using the Student *t* test if a normal distribution was proven and the Mann-Whitney *U* test otherwise. Categorical variables were analyzed applying the χ^2 test or the Fisher exact test, when applicable. Data were analyzed using the SPSS statistical software package release 22.0 (SPSS Inc., Chicago, Illinois) and Stata software, version 14.0 (Stata Corp, College Station, Texas).

Ethical aspects

The study was designed and performed according to the Helsinki declaration. The ethics committee of the Hospital Universitario Puerta del Mar, Cadiz (Spain) approved the study. Informed consent was obtained from all patients for being included in the study.

Results

Incidence of lymphoma

This analysis included 755 HIV-HCV coinfecting patients, being followed up for a median of 24 years (IQR 19–28 years). Prior to HCV therapy (first period), patients had been followed-up for a median of 16 years (IQR, 12–20 years). After ending HCV therapy (second period), patients were followed-up for a median of 10 years (IQR, 6–13 years). Patients' characteristics are shown in Table 1.

A total of 13 lymphomas was diagnosed [LIR (95% CI), 0.72 (0.33–1.11) \times 1000 PY. Time HIV-to-lymphoma (median, IQR), 16 years (12–20)]. Nine of them were NHL [LIR (95% CI), 0.50 (0.17–0.82) \times 1000 PY. Time HIV-to-lymphoma, 15 years (11–19)] and four HL [LIR (95% CI), 0.22 (0.04–0.44) \times 1000 PY. Time HIV-to-lymphoma, 19 years (14–22)]. In four patients, diagnosis of NHL was made previous to anti-HCV therapy [LIR (95%CI), 0.33 (0.00–0.65) \times 1000 PY] and in the other five individuals after HCV therapy [LIR (95%CI), 0.68 (0.08–1.26) \times 1000 PY]. There was no significant difference in LIR between both periods

($p > 0.05$), whereas did exist a significantly longer time from diagnosis of HIV to that of lymphoma [patients who developed it prior to anti-HCV therapy, 11 years (7–15); patients who developed it after anti-HCV therapy, 19 years (15–21), $p < 0.001$]. Three patients who developed NHL after anti-HCV therapy had attained SVR [LIR (95%CI) 0.53 (0.00–1.12) \times 1000 PY], whereas the other two did not show it [LIR (95%CI) 0.32 (0.00–0.76) \times 1000 PY] ($p > 0.05$).

Characteristics of lymphomas

Individual characteristics of patients with lymphoma are presented in Table 2. All of them were male, with a median age at diagnosis of 47 years (range 38–66). CD4+ T cell count at diagnosis of lymphoma was 457/mm³ (IQR 255–569), with only two cases with values lower than 200/mm³. Although all the patients were under ART, four individuals had not reached an undetectable HIV load at the diagnosis of lymphoma.

Four cases of HL were diagnosed. All of them received ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) as the initial schema of therapy. Only one patient relapsed, attaining complete response after CEP [CCNU (lomustin), etoposide (VP-16), and prednisone] combination. There was no death related with the HL, although one of these patients was dead as a consequence of HCV-liver cirrhosis complications.

Nine cases of NHL were diagnosed. In three patients, NHL presented as an extranodal location, in one of them as primary brain lymphoma. The more frequent histology was DLBCL. With the exception of primary brain lymphoma, CHOP (ciclofosfamida, adriamicina, vincristina, prednisone), combined or not with rituximab, was the most frequent initial therapy. Other treatment combinations were used in two patients due to relapse. Seven of them were in complete remission 24 and 120 months after ending the chemotherapy.

Discussion

In this cohort of HIV-HCV coinfecting patients, an incidence of lymphomas in the range of other series analyzing this topic in recent years was detected [2]. Histologic types diagnosed in our population are similar to those described in HIV-infected patients [16, 17]: coincident with a CD4+ T cell count relatively conserved, HL is described. DLBCL predominates among NHL. No case of marginal-type or lymphoplasmatic lymphoma was detected in our series. Response to first-line therapy of lymphomas, combined with ART, was observed in the majority of cases, as it has been previously communicated [18, 19].

The objective of this work was to analyze the influence of anti-HCV on incidence rate of lymphomas in HIV-HCV coinfecting patients in treatment with ART. The incidence of

Table 1 Differential characteristics of HIV-HCV coinfecting patients in function of the absence or presence of diagnosis of lymphoma

Characteristic	HIV-HCV coinfecting patients diagnosed of lymphoma (n = 13)	HIV-HCV coinfecting patients not diagnosed of lymphoma (n = 742)	p value
Age at entry (years) ^a	33 (28–41)	27 (22–33)	0.013
Sex male (n, %)	13 (100)	567 (76)	0.047
IDU as HCV transmission risk (n,%)	12 (92)	364 (49)	0.002
Baseline HIV RNA load (copies/ml) ^a	80,812 (12860–361,240)	50,340 (19000–1,514,000)	0.162
Baseline CD4+ T cells/mm ^{3a}	162 (3–405)	146 (57–250)	0.128
CD4+ T cells/mm ³ at diagnosis of lymphoma, dead (other cause) or end of follow-up ^a	457 (255–569)	508 (336–698)	0.337
CDC stage C (n,%)	12 (92)	299 (41)	<0.001
Antiretroviral therapy at diagnosis of lymphoma or end of follow-up (n,%)	13 (100)	742 (100)	1.000
Reverse transcriptase inhibitor, nucleos(t)ide HIV-treatment backbone (n,%)			
Tenofovir + Emtricitabine	7 (58)	386 (52)	0.881
Abacavir + Lamivudine	2 (8)	156 (21)	0.879
Others	4 (31)	200 (27)	0.994
Third antiretroviral drug (n%)			
Reverse transcriptase inhibitor, non nucleoside	3 (25)	245 (33)	0.646
Protease inhibitor	9 (67)	467 (63)	0.860
Integrase inhibitor	1 (8)	30 (4)	0.962
HCV genotype (n,%)			
1	9 (69)	389 (52)	0.356
2	0 (0)	12 (2)	0.511
3	2 (15)	162 (22)	0.826
4	0 (0)	147 (20)	0.151
Mixed	2 (15)	32 (4)	0.217
HCV RNA load previous to HCV therapy (UI/ml) ^a	3,266,369 (748215–8,285,715)	1,271,454 (303750–3,872,180)	0.149
Cirrhosis (n,%)	0 (0)	138 (18)	0.016
Sustained HCV response (n,%)	6 (46)	358 (48)	0.896

IDU injection drug user

^aData are provided as median (interquartile range)

lymphomas, especially NHL, was similar when compared the first period of study (follow-up from HIV diagnosis to anti-HCV therapy) with the second period of study (from ending HCV therapy to the end of follow-up) and when compared those patients with SVR to anti-HCV therapy with the rest of patients. In other words, anti-HCV therapy did not influence in the incidence rate of lymphomas within this population. This finding was apparently contrary to those detected in HCV-infected patients without HIV coinfection, in which treatment of HCV infection was associated to a decrease in the incidence of lymphomas [8].

The situation in HIV-HCV coinfecting patients is different to that of HCV mono-infected individuals. Firstly, HIV infection itself is associated with an increased incidence of lymphomas [1–3]. Secondly, epidemiological studies associating HCV to lymphomas in HIV-HCV coinfecting patients have communicated contradictory results: the percentage of NHL attributable to HCV in these patients ranges between 0% and

50% [9–12]. Thirdly, an association between lymphoma and Epstein-Barr virus (EBV) is well-established [1]. A higher proportion of EBV-infected individuals among HCV-HIV coinfecting patients from those series with a significant relation between HCV and lymphoma could explain the epidemiological differences.

Proliferation of specific B cell clones because of chronic antigenic stimulation sustained by HCV is the proposed mechanism that drives the HCV-mediated pathogenesis of B cell lymphoma [20, 21]. We suggest an alternative mechanism: the possibility of an HCV-induced potentiation of EBV lymphomagenesis. BZLF1 mRNA, a starter molecule of EBV reactivation, was detected in peripheral blood mononuclear cells from a significantly higher proportion of patients infected with HCV compared with healthy subjects. The BZLF1 mRNA disappeared following anti-viral therapy [22]. EBV seropositivity was not analyzed in our sample.

Table 2 Characteristics of lymphomas diagnosed in HIV-HCV coinfecting patients

Case	Age (years)/sex	Histology	Time from HIV diagnosis (years)	Time from ending HCV therapy (years)	Sustained virological response to HCV therapy	Primary location	Extension (Lugano classification)	CD4 + T cells/mm ³ at diagnosis of lymphoma	HIV RNA load <50 copies/ml at diagnosis of lymphoma	Lymphoma treatments	Results of lymphoma therapy	Time of follow-up since the end of lymphoma therapy (months)	Death
1	45/M	LH, MC	17	-3	Yes	Adenopathy II		257	No	ABVD	CR	60	No
2	53/M	LH, MC	20	2	Yes	Adenopathy II		463	Yes	ABVD	CR	60	No
3	42/M	LH, LR	22	-3	Yes	Adenopathy I		800	Yes	ABVD	CR	27	No
4	38/M	LH, MC	12	-3	No	Adenopathy IV		133	No	ABVD CEP	PR CR	48	Yes (Liver related)
5	44/M	NHL, DLBCL	19	6	No	Adenopathy III		396	Yes	R-CHOP	CR	72	No
6	49/M	NHL, DLBCL	13	-3	No	Adenopathy III		457	No	CHOP	CR	36	No
7	38/M	NHL, DLBCL	15	-6	No	Adenopathy III		562	Yes	CHOP R-ESHAP R-miniBEAM	CR, relapse CR, relapse CR	36	No
8	48/M	NHL, DLBCL	16	-10	No	Adenopathy I		575	Yes	CHOP	CR	55	No
9	45/M	NHL, FL 1	22	3	Yes	Adenopathy III		616	Yes	R-CHOP	CR	24	No
10	53/M	NHL, DLBCL	18	6	No	Extranodal IV		562	Yes	R-CHOP	CR	36	No
11	52/M	NHL, DLBCL	11	-3	No	Adenopathy III		278	Yes	R-CHOP ESHAP	CR, relapse CR	36	No
12	44/M	NHL, PBL	11	3	Yes	Extranodal		154	Yes	Intrathecal MTX + RT	PR	18	No
13	66/M	NHL, DLBCL	3	3	Yes	Extranodal IV		253	No	CHOP	CR	120	No

M male, *F* female, *NHL* Non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *DLBCL* diffuse large B-cell lymphoma, *FL 1* Follicular lymphoma grade 1, *LR* classic HL, rich in lymphocyte, *MC* mixed cellularity, *PBL* primary brain lymphoma, *ABVD* doxorubicin, bleomycin, vincristine and dacarbazine, *CHOP* cyclophosphamide, adriamycin, vincristine, and prednisone, *CEP* lomustin, etoposide (VP-16) and prednisone, *MTX* high-dose methotrexate, *RT* whole-brain radiotherapy, *R-CHOP* rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone, *R-ESHAP* rituximab, etoposide (VP-16), methyl-prednisolone, cytarabine (Ara-C) and cisplatin, *R-miniBEAM*, BCNU, etoposide, cytosine arabinoside, melphalan, *CR* complete response, *PR* partial response, *NR* no response

The retrospective nature of the study could be a limitation of this work. However, patients in the HEPAVIR cohort have been prospectively followed-up according to a uniform protocol, limiting the variability of the results. The size of the sample could also decrease the possibility of demonstrating differences between the considered periods (pre- and post-HCV therapy), but it is remarkable that the incidence rate in the second period is even higher than in the time previous to anti-HCV therapy, possibly implicating a longer time of HIV infection evolution as the main factor in the lymphoma development. Another limitation could be the fact that HCV infection would be not concurrent with HIV infection. However, it is improbable. Indeed, it is accepted that HCV infection occurs at the date of the first transfusion or during the first year of intravenous drug injection in 90% of patients, whereas HIV infection occurs later [23]. In several series and meta-analyses, the duration of HIV or HCV infection has been established as in the present work [24, 25].

In conclusion, our series has shown that *INF + RBV as anti-HCV therapy* does not modify the incidence rate of lymphomas in a population of HIV-HCV coinfecting patients.

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Compliance with ethical standards

The ethics committee of the Hospital Universitario Puerta del Mar, Cadiz (Spain) approved the study. Informed consent was obtained from all patients for being included in the study.

Conflict of interest The authors declare that they have no competing interests.

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