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Antiviral treatment in patients with indolent B-cell lymphomas associated with HCV infection: a study of the Fondazione Italiana Linfomi

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Key Message: "Present study demonstrates that antiviral treatment plays an anti-lymphoma activity in HCV-associated indolent B-cell lymphomas and that the use of antiviral treatment at any time during the life of these patients is clearly associated with improved outcome. Despite the limitations related to retrospective nature of the study, in absence of effective methodological alternatives, present data may impact the standard of care."

Abstract

Background Tumour regression after antiviral therapy (AT) is in favour of an etiological role of hepatitis C virus (HCV) in non-Hodgkin's B-cell lymphomas (NHL).

Patients and methods We performed a cohort study of 704 consecutive HIV-negative, HCV-positive patients with indolent NHL diagnosed and treated from 1993 to 2009 in 39 centers of the Fondazione Italiana Linfomi; 134 patients were managed with AT for lymphoma control.

Results For entire cohort, 5-yr overall survival (OS) was 78% (95%CI: 74-82%) and 5-yr progression-free survival (PFS) was 48% (95%CI: 44-53%). In multivariate analysis, use of AT during the patients' life had positive impact on OS. Fourty four of the 100 patients treated with first-line AT achieved a CR and 33 a partial response (PR). HCV-RNA clearance was achieved in 80 patients and was related to lymphoma response. At a median follow-up of 3.6 years, 5-yr PFS was 63% (95%CI: 50%-73%). CR + PR rate was 85% with AT as second-line treatment.

Conclusion AT produces HCV-RNA clearance and consequent tumour regression in most patients with HCV-related indolent NHL. AT used at any time is associated with improved OS. Consequently, AT can be considered an option for patients with indolent lymphomas who do not need immediate cytoreductive treatment.

Key words: HCV, indolent lymphoma, antiviral treatment, outcome

INTRODUCTION

In addition to liver involvement, hepatitis C virus (HCV) infection has been linked to lymphoproliferative disorders and the role of HCV infection in lymphomagenesis may be related to chronic antigenic stimulation of the virus [1].

Several epidemiological studies have been performed since the mid '90s to investigate the link between HCV and non-Hodgkin's lymphoma (NHL). Systematic concluded that HCV prevalence in patients with B-NHL is higher with respect to general population [2]. In subtype-specific analyses, HCV prevalence was associated with marginal zone lymphoma (MZL) (OR=2.47), diffuse large B-cell lymphoma (DLBCL) (OR=2.24), and lymphoplasmacytic lymphoma (LPL) (OR=2.57) [3].

Interestingly, Kawamura et al demonstrated that sustained virologic response induced by IFN therapy protects against the development of malignant lymphoma in HCV-infected patients [4].

The regression of HCV-associated lymphoma with antiviral treatment (AT) alone is the strongest argument in favour of an aetiological link between lymphoma and infection [5, 6].

In relation to the relatively low number of patients treated with AT so far, the impact of this approach on the outcome of indolent lymphomas associated with HCV infection needs to be confirmed. To this task, a survey ("HCV-LNH outcome survey") was initiated in Italy under the sponsorship of the Fondazione Italiana Linfomi (FIL) in 2010 to better define the outcome and the efficacy of treatments of HCV-positive NHL. Moreover, we analyzed separately the 134 patients managed with AT as anti-lymphoma strategy.

METHODS

Study design

In the nationwide database of Fondazione Italiana Linfomi (FIL) (before 2012 named Intergruppo Italiano Linfomi, IIL), we identified 704 HCV-positive (serology and/or HCV-RNA), HIV-negative patients affected by indolent NHL diagnosed between 1993 and 2009 in 39 centers members with available information about treatment. HCV infection is a substantial health problem in Italy and majority of patients with NHL are evaluated for HCV infection.

HCV-positive cases were 15% of all registered cases with available HCV serology from participating centers; HCV serology was not available for 19.5% of all diagnosed cases in the examined period. We included also cases of mantle cell lymphoma with an indolent course. Since 2000 FIL/IIL centers shared homogeneous procedures for lymphoma diagnosis, staging, response assessment, and follow-up. Before 2000, minimal requirements of homogeneity were adopted. A central pathology review was not formally performed; however, participating centers are all characterized by high rate of lymphomas diagnosis and local pathologists systematically participate in the activities of updating the diagnostic procedures of the FIL. All lymphoma cases are consecutively included and followed by centers participating to the FIL.

The database of HCV-positive indolent NHL was analyzed to establish HCV infection features, distribution of lymphoma categories, clinical presentation, natural history, therapeutic management, outcome, and prognostic factors.

We also analysed in detail virological and lymphoma response and outcome of 134 patients who received AT both as first-line (*n*=100) and second-line (*n*=34) anti-lymphoma treatment: all these patients did not need immediate citoreductive therapy at start of AT.

Approval for this study, which was based on the use of archival data, was obtained from the Institutional Review Board. The report was prepared in accordance with the STROBE statement [7]. Data management and analysis were performed in accordance with the ethical guidelines of the FIL and the tenets of the Declaration of Helsinki of 1964, as revised in 2000. All patients gave informed consent.

End-points and variables

The primary outcome measure was overall survival (OS); secondary endpoints were progression free survival (PFS), complete remission (CR) and partial remission (PR) rates. OS was taken from diagnosis until death from any cause; patients who had not died were censored at the date of their last follow up visit. PFS was defined as the time from start of treatment until lymphoma progression or initiation of new treatment, or death [8]. Several variables were included in the analysis (Table 1; Supplemental Table 1), including use of AT

at any time during a patient's life.

For patients analyzed for anti-lymphoma activity of AT, CR was defined by the complete disappearance of all detectable sites and symptoms; PR was defined as a more than 50% reduction. Responses different from CR/PR were defined as stable disease (SD); progressive disease (PD) was considered an increase in size of more than 25% of previously documented disease or the appearance of new lesions. Specific examinations have been performed for response assessment in peculiar clinical presentations (i.e. paraprotein level when present before AT, endoscopy for gastric MALT lymphoma). For these patients OS and PFS was calculated from start of therapy.

Statistical analysis

Association between categorical variables was tested by using the Pearson χ^2 test or the Fisher's exact test. Difference in mean values of quantitative variables between two independent groups was tested by using t test for unpaired data. The Kaplan-Meier product-limit method was used to estimate OS and PFS.

The adjusted association of AT with OS and PFS was estimated by means of backward stepwise multivariate Cox regression models, after checking for the applicability assumptions. The significance value for exclusion was set at 0.10, but both models were 'forced' to keep AT and diagnosis. AT was analyzed as a time-dependent covariate. Unadjusted and adjusted hazard ratios (HR) with 95% confidence interval (95%CI) are provided. The limit of significance for all analyses was defined as a *p* value ≤0.05. All computations were performed using Stata 12.1 (2007).

RESULTS

Clinical and virological features

Clinical features of 704 patients with indolent lymphoma associated with HCV infection are summarized in Table 1. There was a prevalence of females and median age was 66 years; MZL was the commonest subtype. Virological features are summarized in Supplemental table 1.

Outcome

Alkylators was first-line treatment in 148 patients (21%), rituximab + alkylators in 49 (7%), CHOP in 106 (15%), R-CHOP in 77 (11%), other chemotherapy regimens in 56 (8%), AT in 100 (14%), radiotherapy 21 (3%), surgery in 21 (3%), antibiotics in 13 (2%), watch and wait in 113 (16%).

324 patients experienced lymphoma relapse or progression at a median follow-up of 3.5 years (range 0.5-17). Five hundred and thirty-nine patients are alive (169 without evidence of disease), with a 5- and 10-yr OS of 78% (95%CI: 74%-82%) and 62% (95%CI: 55%-67%), respectively (Figure 1); 5- and 10-yr PFS of 48% (95%CI: 43%-53%) and 30% (95%CI: 25%-36%), respectively (Figure 2). Causes of death were: lymphoma 65%, cardiovascular events 12%, liver disease 9%, infection 6%, other neoplasia 6%, other causes 2%.

Univariate and multivariate analysis

In univariate analysis AT showed a significant association both with OS and PFS (Supplemental table 2). Furthermore, age>60 yrs, B symptoms, ECOG>1, albumin<3.5 g/dl and increased LDH were also associated with OS and PFS, while Ann Arbor stage III-IV, absence of cryoglobulinemia and of symptomatic cryoglobulinemia and the presence of cirrhosis were associated only with OS (Supplemental table 2).

Despite the multivariate analysis has shown a significant association of age>60 years, cirrhosis, cryoglobulinemia and albumin<3.5 g/dl with OS, in multivariate analysis AT retained a protective effect with OS (Table 2, Figure 3). On the contrary, the protective effect of AT on PFS was not confirmed after adjustment for confounders.

Anti-lymphoma antiviral treatment

One hundred and thirty-four patients received AT for lymphoma control: 100 patients received AT as first-line option, while 34 patients received AT as second-line treatment following a previous therapeutic failure. AT consisted of IFN in 47 patients (plus RBV in 36) and peg-IFN in 87 (plus RBV in 82). Median age was 60 yrs (range 23-80 yrs) with no

difference between patients treated with AT as first or second line (p=0.07). Histological, virological and hematological features of the 134 patients are summarized in Table 3.

First-line antiviral treatment: tolerability and activity

Among 100 patients treated with AT as first line (33 with IFN and 67 with peg-IFN), 60 were affected by MZL. HCV genotype was 2 in 52 patients and 1 in 37. Median duration of first-line AT was 7 months (range 2-48). Eighty-seven patients completed the planned AT; 6 patients discontinued due to toxicity while 7 patients interrupted AT early due to lymphoma progression and lack of virological response. HCV-RNA clearance was achieved in 80 patients (80%).

Fourty four (44%) of patients achieved CR and 33 (33%) PR, with an ORR of 77% (95%CI: 69%-85%); 14 (14%) had SD. The median response duration was 33 months.

Lymphoma response was related to achievement of HCV-RNA clearance (p=0.003) (Supplemental table 3). Lymphoma response was not statistically different between patients with MZL and non-MZL (ORR: 82% vs. 70%) whereas it was lower in splenic MZL respect to other MZL cases (ORR: 65% vs. 92%; p=0.02). ORR was 83% in genotype 2 carriers and 70% in genotype 1 carriers (p =0.3).

At a median follow-up of 3.6 years, 9 patients progressed and 13 experienced lymphoma relapse after initial response to AT, with a 5-yr PFS of 63% (95%CI: 50%-73%)(Figure 3, panel B). 5-yr PFS for patients not treated with AT as first line was 45% (95%CI: 49%-50%) and was statistically shorter in comparison to treated patients (HR=0.56, 95%CI: 0.39-0.80, p=0.001).

Eighty-nine patients treated with first-line AT are alive, with a 5-yr OS of 92% (95%CI: 83%-96%) (Figure 3, panel A); only two patients died for lymphoma. The other causes of death were: hepatocellular carcinoma (n=3), infections (n=2), and cirrhosis, herpetic encephalitis, myelodysplastic syndrome, and suicide (n=1 for each). 5-yr OS for patients not treated with AT as first line was 75 % (95%CI: 71%-80%) and was statistically shorter in comparison to treated patients (HR=0.39, 95%CI: 0.20-0.73, p=0.004). OS did not differ according to genotype, lymphoma category and serum levels of albumin, β_2-microglobulin

and LDH. Impact of type of IFN (adjusted for levels of albumin, β_2-microglobulin and LDH) remained significant also in multivariate analysis (peg-IFN vs IFN, HR=0.08, 95%CI: 0.01-0.81, *p*=0.03).

Second-line antiviral treatment

Nineteen (56%) of the 34 patients treated with second-line AT (14 with IFN and 20 with peg-IFN) for relapse after a conventional first-line therapy achieved a CR and 10 (29%) a PR, with an ORR of 85% (95%CI: 73%-97%). HCV clearance was achieved in 22 patients (67%). The median response duration was 26 months. At a median follow-up of 4.1 yrs, 4 patients progressed and 6 experienced lymphoma relapse after initial response to AT, with a 5-yr PFS of 63% (95%CI: 50%-73%).

DISCUSSION

To the best of our knowledge, this is the largest multicenter study focused on the anti-lymphoma efficacy of AT. Indeed, no reported study included more than 20 cases and related literature consists of around 100 patients treated with this strategy [9].

The present study shows that anti-lymphoma activity of AT is associated with viral load clearance and that AT is an active therapeutic option in these patients. The use of AT at any time during the life of these patients seems to be associated with improved outcome, which enforces the recommendation that AT must be considered as first-line approach for patients with indolent lymphomas who do not need immediate conventional treatment.

Major limitations of the present study are related to retrospective nature of the observation and the possible selection, loss-to-follow-up, referral bias of patients treated with AT; however, despite these aspects, reported cases are consecutively observed in centers and the decision of using AT is uniformly applied in all centers. Although PFS results might have been biased by the retrospective nature of this study, the significant results observed for OS make clinically relevant the present findings. Considering the particular nature of this subset of lymphoma and the objective difficulty to perform prospective trials in significantly wide cohort of patients, our data may impact the standard of care.

It is possible that there are potential confounding factors that influence the difference in OS between the AT group and those who did not have AT, which we did not have data on (for the multivariate analysis in Table 2). However, the effect was so large (HR=0.33), that it is unlikely other important confounders could explain this size of effect.

About 10 years ago, some reports attested the efficacy of AT in HCV-related SMZL [5, 10]. A previous study from our group extended this experience to a cohort of 13 patients with indolent lymphoma even different from SMZL [6]. Although that study included a relatively small number of patients, results showed no significant differences within different lymphomas categories and suggested that lymphoma response to AT was related to viral load decrease or disappearance.

ORR in the present group of patients who received upfront AT is similar to that reported in our first study (77% vs. 74%) [12], with a slightly lower CR rate (44% vs 58%). Interestingly, this wide study is in line with previous studies [10-12] suggesting that HCV-RNA clearance is a *conditio sine qua non* to attain lymphoma response.

A relevant contribution of the present study regards the demonstration that tumour regression after AT can be obtained in diverse lymphoma categories. In fact, response rate was not different between MZL and non-MZL.

In the present study, few patients were lymphoma-unresponsive to AT, which could be related to HCV-independent phase of disease in which antigenic trigger is no longer necessary for lymphoproliferation, possibly because of additional genomic events. Although a relation between genotype and lymphoma response was not observed, genotype 1 carriers seemed to be less responsive than genotype 2 carriers. For the past decade, only 40–45% of these patients achieved a sustained virological response when treated with peg-IFN/RBV [11]. Although the direct anti-lymphoma properties of IFN cannot be ruled out [12], it should be underlined the clear association between the lymphoma regression and the clearance of HCV. A possible evolution could be the addition of rituximab to the standard regimen as reported in HCV-associated cryoglobulinemia patients [13]. Since rituximab alone therapy has also been shown to induce lymphoma regression in patients with MZL, the safety and efficacy of combined AT and rituximab in patients with HCV-related MZL should be examined.

Finally, IFN-free regimens with direct antiviral agents only [14], could consent the access to AT also for HCV-positive NHL patients with contraindications to IFN use. In addition, considering the anti-proliferative properties of IFN [12], lymphoma response could definitely demonstrated that lymphoma regression is strictly linked to the HCV eradication.
Overall, the present study could be considered as a good historical control group for future prospective trials.

Considering the entire series of 704 patients, AT had a positive prognostic influence on OS. Interestingly, a study has shown that HCV-infected patients who obtained a sustained virologic response following AT had an HR of lymphoma risk significantly lower than patients who did not receive AT [4].
Thus, our data, together with Japanese findings [4], strongly support the efficacy of AT in indolent NHL associated with HCV infection. It remains to clarify the benefit of AT after (immuno)-chemotherapy if AT is not feasible (for instance, in case of symptoms and/or high tumour burden).

In conclusion, the present study shows anti-lymphoma activity of AT in a large series of HCV-infected patients with indolent NHL. Consequently, this strategy could be considered the first-line option for patients with indolent lymphomas who do not need for immediate conventional treatment. The observation that AT used at any time during the patients' life is associated with improved OS enforces such a therapeutic opportunity and suggests a relevant advantage of AT in this setting beyond the objective detection of lymphoma regression.

Figure legends

Figure 1. Overall survival (panel A) and progression-free survival (panel B) of entire series of 704 patients with HCV-associated indolent lymphoma

Figure 2. Overall survival according to the use of antiviral treatment at any time

Figure 3. Overall survival (panel A) and progression-free survival (panel B) of 100 patients treated with AT as first line anti-lymphoma treatment

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Conflict of interest disclosure:

Authors have declared no conflicts of interest.

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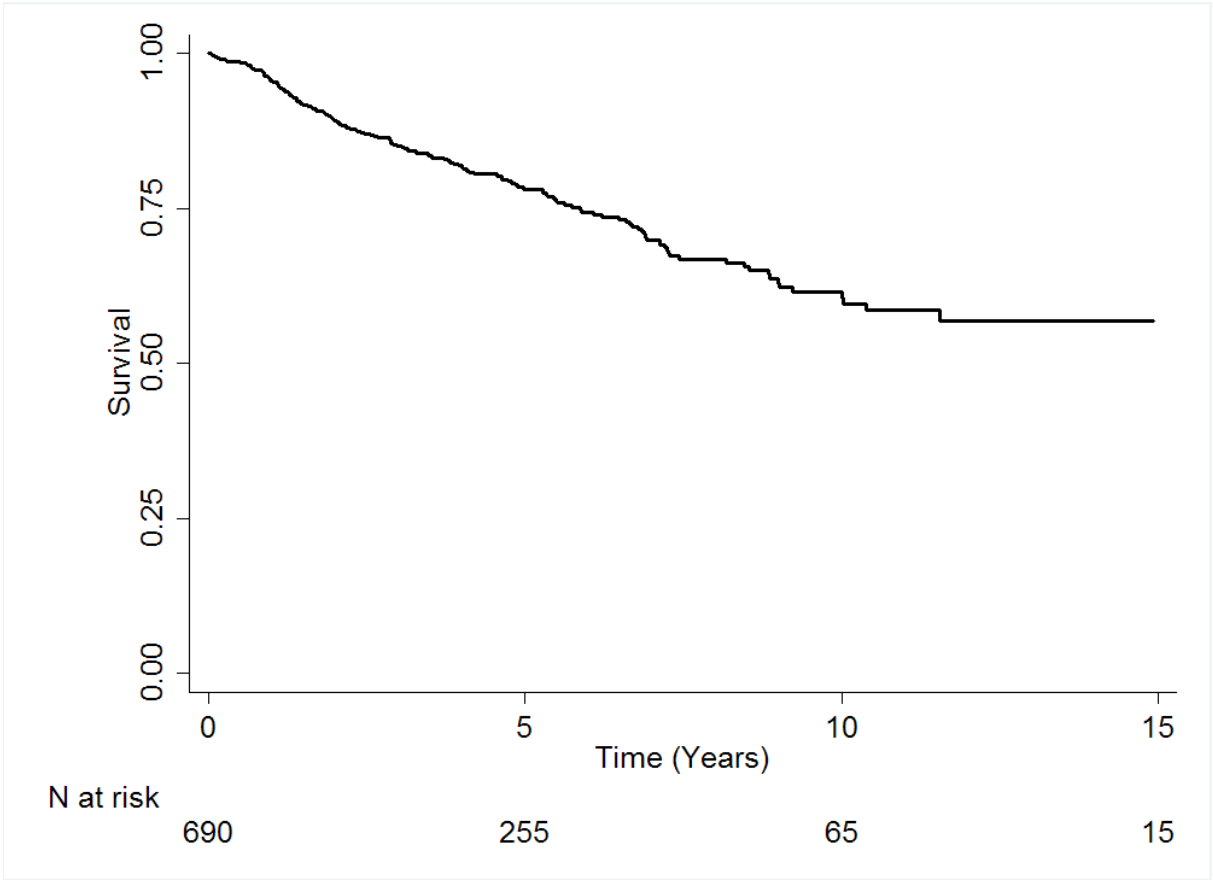

Figure 1 Panel A

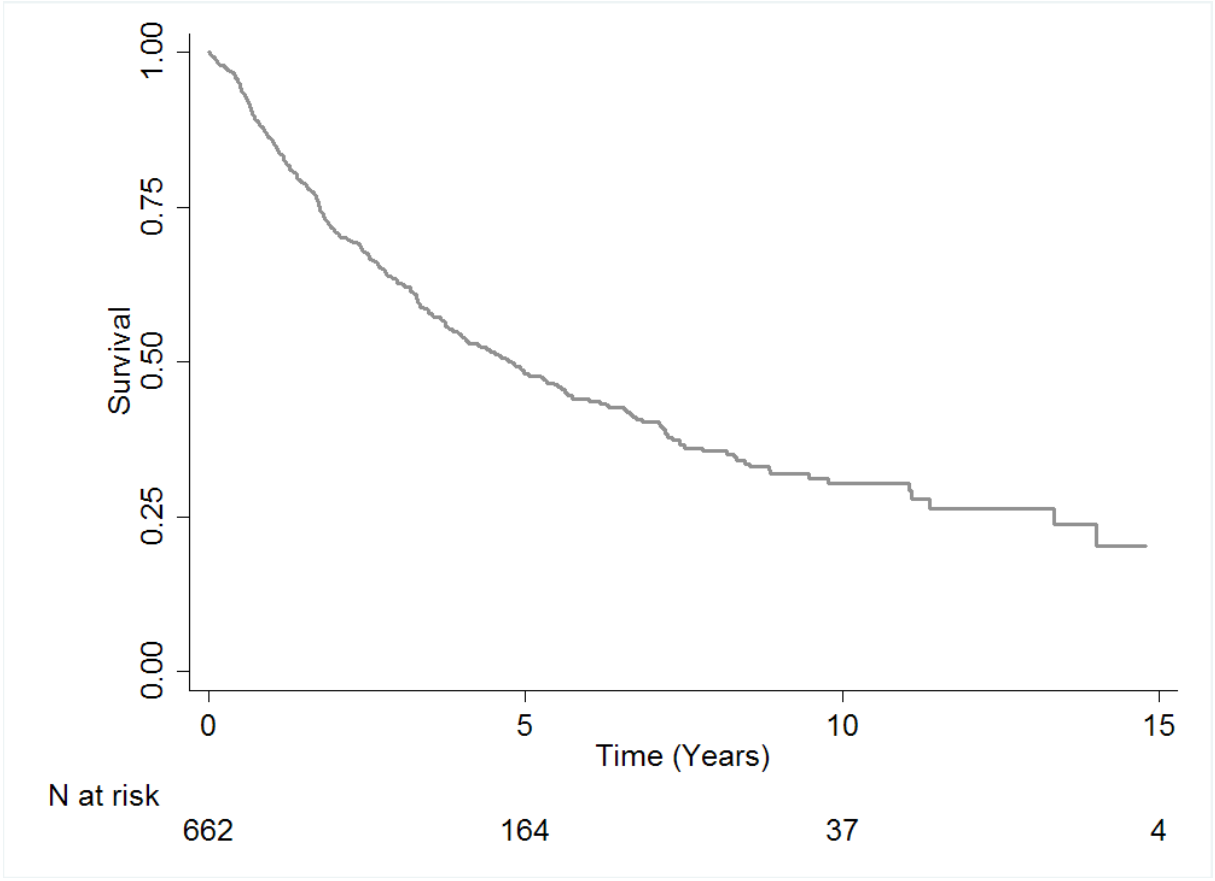

Figure 1 Panel B

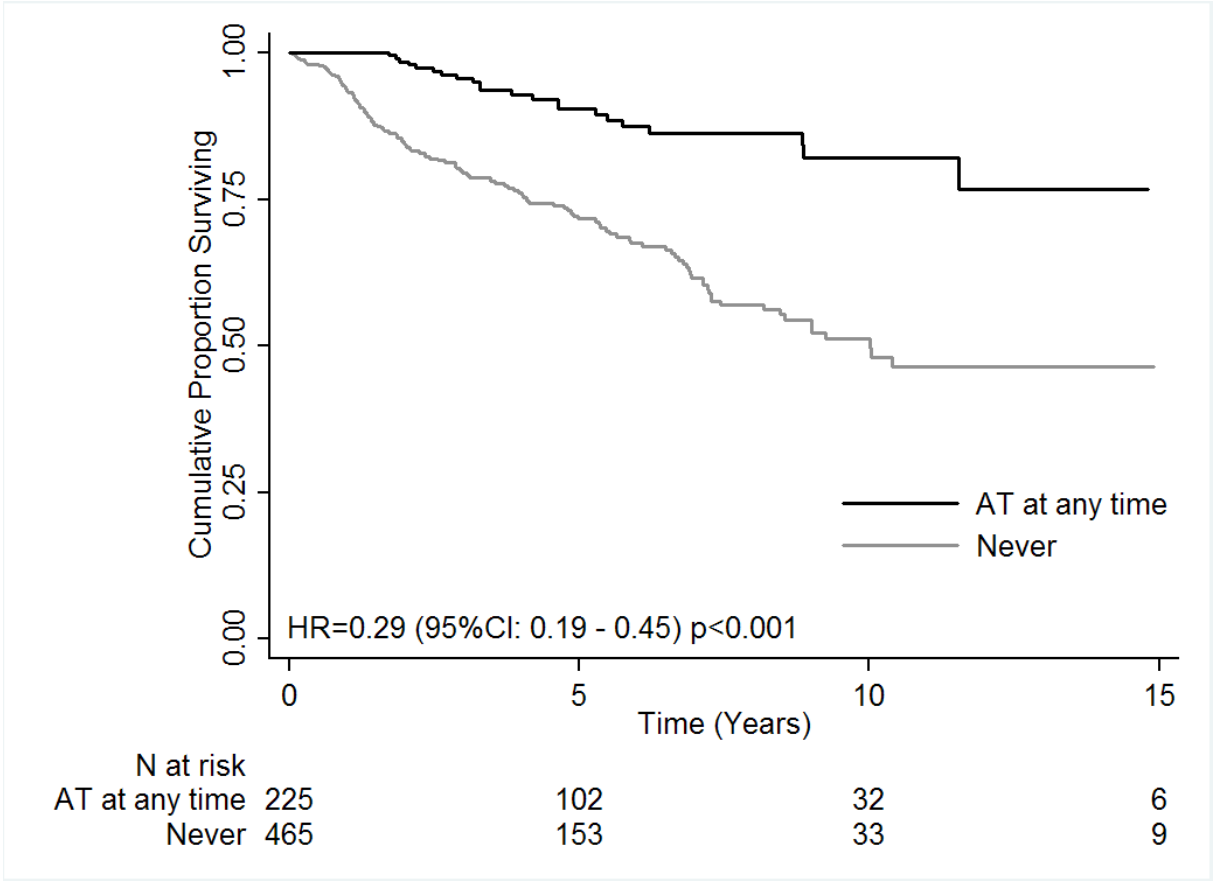

Figure 2

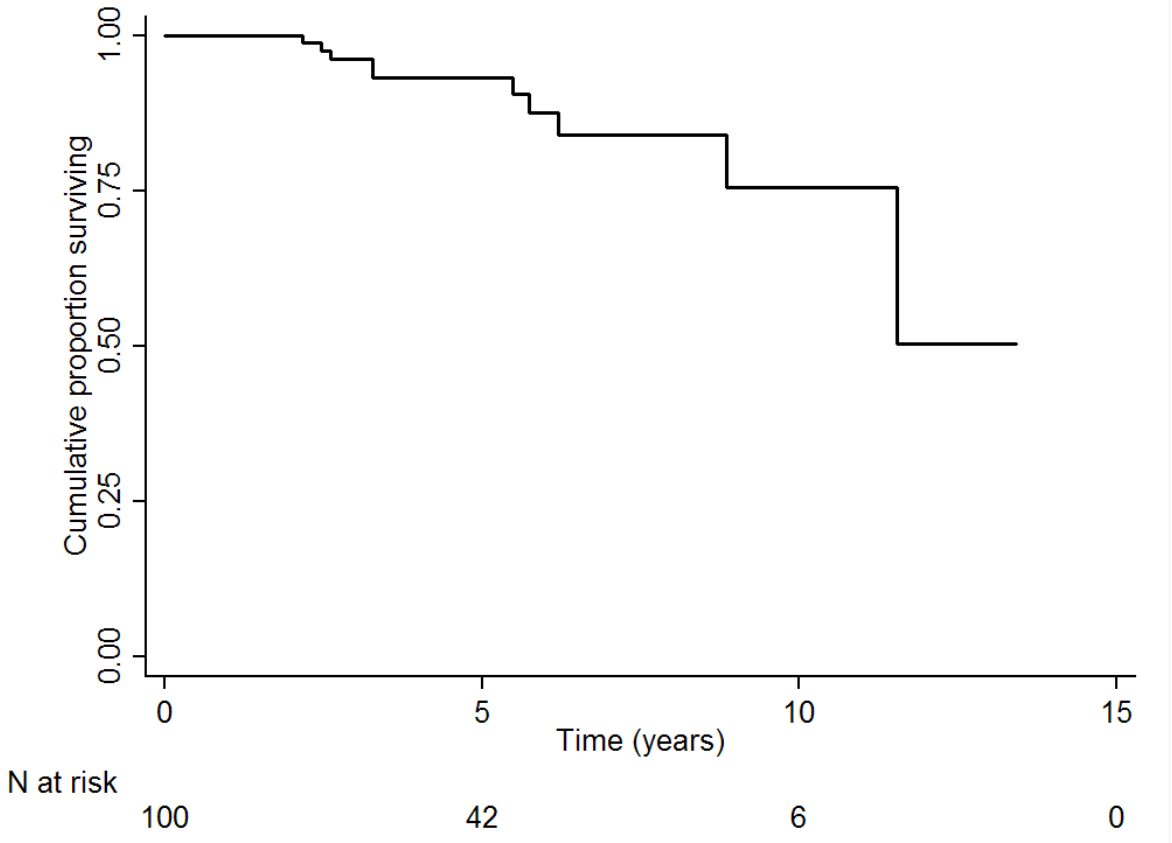

Figure 3 Panel A

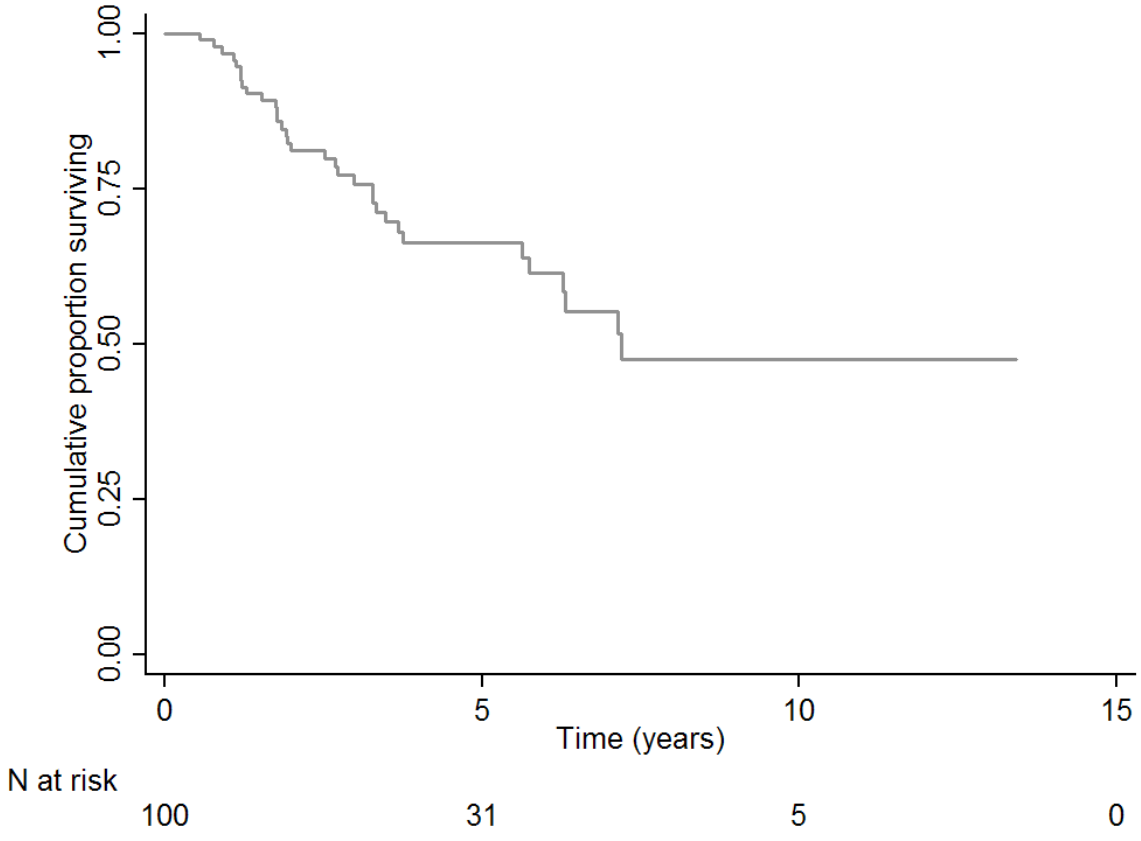

Figure 3 Panel B

Table 1 – Comparison of clinical features of patients who underwent antiviral therapy as anti-lymphoma treatment with respect to those who did not. Counts (n) and percentage frequencies (%) with the Pearson's χ^2 test and the significance level (p-value) are reported.

			Antiviral therapy as anti-lymphoma treatment				
			Yes (134)		No (570)		
	n	%	n	%	n	%	Test and p-value
Male/Female	289/415	41/59	57/77	43/57	232/338	41/59	χ^2=0.2 *p*=0.698
Age > 60 years	483	69	70	52	413	73	χ^2=21.5 *p*<0.001
Histotypes							χ^2=27.7 *p*<0.001
Follicular lymphoma	134	19	12	9	122	21	
MALT MZL	157	22	29	22	128	22	
Primary nodal MZL	59	8	13	9	46	8	
Splenic MZL	137	20	36	27	101	18	
Small lymphocytic lymphoma	37	5	4	3	33	6	
Lymphoplasmacytic lymphoma	53	8	10	7	43	8	
Indolent mantle-cell lymphoma	30	4	1	1	29	5	
Indolent B-cell NHL NOS	97	14	29	22	68	12	
Ann Arbor stage III+IV	550	79	116	87	434	77	χ^2=6.3 *p*=0.012
Extranodal disease	271	42	80	60	191	38	χ^2=21.4 *p*<0.001
Liver involvement	53	8	16	12	37	7	χ^2=3.1 *p*=0.080
ECOG 2-3	65	10	6	4	59	11	χ^2=5.1 *p*=0.025
LDH > UNL	164	24	31	24	133	24	χ^2=0.0 *p*=0.921
Albumin < 3,5 mg/dl	100	16	16	13	84	17	χ^2=1.0 *p*=0.308

MZL = marginal zone lymphoma; MALT = mucosa-associated lymphoid tissue; NOS=not otherwise specified; LDH = lactate dehydrogenase; UNL = upper normal limit

Table 2 - Predictive model for OS and PFS derived from multivariate backward stepwise Cox analysis, considering antiviral treatment as a time-dependent covariate. The mutually adjusted hazard ratios (HRs) with the 95% confidence interval (95%CI) and the significance level (p-value) are reported. HRs are also adjusted for diagnosis.

	HR	95%CI	*p*-value
OVERALL SURVIVAL			
Antiviral treatment	0.21	0.06-0.73	0.014
Age>60 years	3.89	1.71-8.85	0.001
B symptoms	1.99	0.88-4.51	0.099
Cirrhosis	2.81	1.24-6.35	0.013
Cryoglobulinemia	0.36	0.15-0.88	0.024
Albumin <3.5 g/dl	3.16	1.64-6.09	0.001
PROGRESSION-FREE SURVIVAL			
Antiviral treatment	0.80	0.48-1.33	0.385
Age>60 years	1.43	0.95-2.17	0.089
ECOG>1	1.64	0.93-2.87	0.085
Albumin <3.5 g/dl	1.55	1.00-2.40	0.050

Table 3- Histological, virological and hematological features of 134 patients with HCV-related indolent B-cell lymphoma treated with antiviral therapy as anti-lymphoma treatment. Counts (n) and percentage frequencies (%) are reported.

	First-line AT (100)		Second-line AT (34)	
	n	**%**	**n**	**%**
M/F	41/59	41/59	15/19	44/56
- Marginal-zone lymphoma	60	60	20	59
Splenic	23	23	12	35
Nodal	12	12	2	6
Extranodal of MALT	25	25	6	18
- Follicular lymphoma	5	5	7	20
- Lymphoplasmacytic lymphoma	7	7	2	6
- Mantle cell lymphoma	0	0	0	0
- Small lymphocytic lymphoma	1	1	3	9
- Indolent B-cell NHL NOS	27	27	2	6
Ann Arbor stage III-IV	90	90	28	82
Elevated β_2-microglobulin	31	53	23	79
Albumin <3.5 g/dl	10	11	6	19
Serum MC	35	35	13	38
HCV genotype				
- 1	37	39	15	50
- 2	52	55	13	43
- 3	5	5	2	7
- 5	1	1	0	0
Cryoglobulinemia	34	34	10	29
Symptomatic cryoglobulinemia	19	56	7	70