Survival in HIV-1 positive individuals with diagnosis of lymphoma compared to general population

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Background

Since the introduction of combined antiretroviral therapy (cART), survival of HIV-associated Lymphoma (Hodgkin and non-Hodgkin) has considerably improved, due to increased response to chemotherapy in people taking cART (1-4). Although even the incidence of HIV-related lymphoma has significantly declined, this condition still represent one of the most prevalent causes of hospitalization occurring in HIV-infected patients even in the era of cART (5) and a major cause of morbidity and mortality (6). The improved prognosis seen in recent years may be due to both the use of more intensive chemotherapy regimens (similar to those used for non HIV-associated lymphoma) and to increased immune recovery and better control of HIV infection itself due to more potent antiretroviral regimens. Nevertheless, whether survival in HIV-infected patients remains different from that observed in the general population with the same type of lymphoma remains to be demonstrated.

Objectives

- To evaluate overall survival after a diagnosis of lymphoma occurring in HIV-infected population (both NHL and HD) compared to those occurring in HIV-uninfected population.
- To identify predictors of mortality among the two studied populations

Methods

All patients with a diagnosis of HIV-L (NHL and HD) observed between January 1, 2000 and December 31, 2013 in the ICONA Foundation cohort and in other four mono-center clinical databases in Italy (UCSC, San Raffaele, INMI, San Gerardo) were included in the analysis. The following data regarding neoplasia were retrospectively collected for each patient diagnosed with a lymphoma: date of lymphoma diagnosis, histo-type, Ann Arbor staging, regimens of chemotherapy, use of rituximab, radiotherapy, response to chemotherapy/radiotherapy, relapse, date of last observation and cause of death. For controls, all patients observed in the same period of observation at UCSC Hematology unit with a diagnosis of lymphoma without HIV infection (nHIV-L) have been included and the same data regarding neoplasia were retrospectively collected.

Analyses were performed stratified by type of lymphoma: 1) for all NHL; 2) in the subset of NHL with diffuse large B-cell lymphoma (DLBCL); and 3) Hodgkin disease (HD). Survival estimates by KM and predictors of OS by multivariable Cox regression after adjusting for some key potential confounders (calendar year, age, gender, International Prognostic Index score, use of rituximab) were obtained (Model B-E, for NHL, model B-D for HD). In a subset of HIV+ and HIV- people for which matching was possible, an individual based matched adjusted analysis was also performed using the same list of confounders as matching factors (Model F for NHL, model E for HD).

Results

A total of 1351 patients with lymphoma were observed in the time period of the study (of a total of 5765 person/years of follow up). Of the participants, 485 (36%) were HIV-L, 866 (64%) were nHIV-L. Median age was 45 years (IQR 39-51) for HIV-L and 54 years (IQR 37-69) for nHIV-L (p<0.001); 74 patients were female (15%) in HIV-L group and 448 (52%) in nHIV-L group (p<0.001). HIV transmission route was PWID in 22%, MSM in 22% and heterosexuals contacts in 29% of HIV-L patients. Median year of lymphoma diagnosis was similar between groups (2008, IQR: 2005-2011 for HIV-L; 2008, IQR: 2004-2011 in nHIV-L). 119 patients (29%) were HCV-Ab positive and 38 (11%) HBsAg positive in the HIV-L group. Baseline tumor characteristics according to HIV status are reported in Table 1.

Among HIV-L, 141 patients (29%) were cART naive at lymphoma diagnosis and started cART during chemotherapy, while 301 patiens (62%) developed lymphoma while there were already exposed to cART; 43 patients (9%) never started cART.

Table 1. Baseline tumor characteristics according to HIV status

	HIV-L	nHIV-L	P value	total
Non Hodgkin Lymphoma, n (%)	314 (34.4)	588 (64.4)		902
IPI score				
Low	42 (13.3)	73 (12.2)	0.04	115 (12.6)
intermediate	105 (33.2)	248 (41.5)		353 (38.6)
High	26 (8.2)	57 (9.5)		83 (9.1)
Histotype				
DLBCL	203(64.6)	559 (95.1)	<0.001	762 (84.5)
SNCCL (Burkitt, Burkitt-like)	84 (26.9)	27 (4.6)		111 (12.3)
IBL	21 (6.6)	2 (0.3)		23 (2.5)
PBL	6 (1.9)	0 (0)		6 (0.7)
First line chemotherapy	294 (95.8)	559 (99.3)	<0.001	853 (98.0)
SNC prophylaxis	147 (81.5)	109 (25.6)	<0.001	256 (41.8)
CHOP, CHOP-like regimens	235 (87.4)	419 (76.7)	0.001	654 (80.3)
Other regimens	83 (26.3)	117 (19.6)	0.020	200 (21.9)
Use of rituximab	173 (66.3)	387 (77.2)	0.001	560 (73.4)
Hodgkin's disease, n (%)	145 (31.7)	278 (32.1)		423 (31.9)
Histotype				
Nodular sclerosing	32(22.2)	203 (69.8)	<0.001	235 (54.0)
Mixed cellular	51 (35.4)	17 (5.8)		68 (15.6)
Lymphocyte-depleted	4 (2.8)	5 (1.7)		9 (2.1)
Lymphocyte-rich	7 (4.9)	17 (5.8)		24 (5.5)
unspecified	50 (34.7)	49 (16.8)		99 (22.8)
IPI score				
Low	18 (12.5)	nd	nd	-
intermediate	36 (25.0)	nd		
High	4 (2.8)	nd		
First line chemotherapy	134 (95.0)	289 (99.3)	0.004	423 (97.9)
ABVD	111 (95.7)	169 (58.5)	<0.001	280 (69.1)
VEBEP	29 (35.8)	0	<0.001	29 (7.8)
BEACOPP	16 (22.9)	58 (20)	0.59	74 (20.6)

Overall survival in the whole population studied according to HIV status

The unadjusted 3-year overall probability of death was significantly higher in the HIV-L group [34%, 95% confidence interval (30–39%) vs. 18%, 95% confidence interval (CI) (16–21%); P<0.001] in the general population. In the HIV-L subgroup who ever started cART, the 3-year probability of death was comparable to that of all HIV-L patients (36%, 95%CI 31-42%).

Adjusted hazard ratios (HR) of death in different Cox regression models are shown in Table 2 for NHL and in Table 3 for HD

Figure 1 . Unadjusted estimates of survival according to HIV status according to type of lymphoma

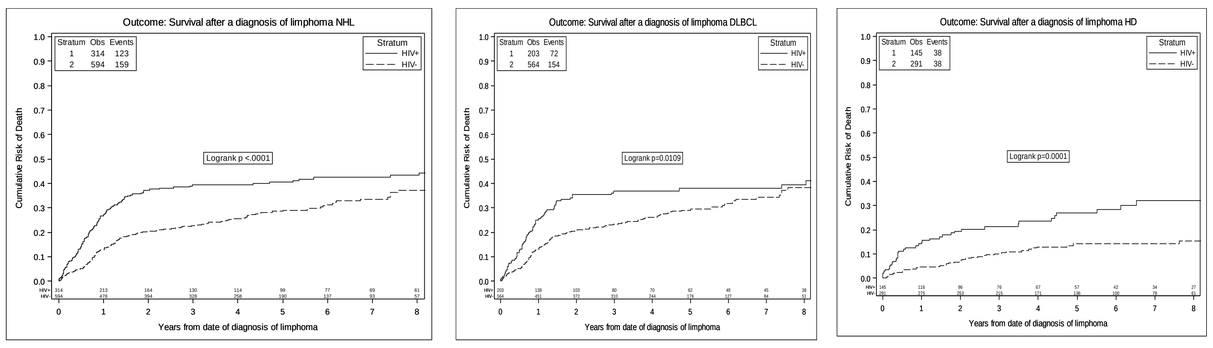

Table 2. Adjusted HR of death from fitting a separate Cox regression model in all NHL (A) and in DLBCL (B)

A

	Relative hazards of death	
	RH of HIV+ vs. HIV- (95% CI)	p-value
Model A		
Unadjusted	2.11 (1.70, 2.61)	<.001
Model B		
Adjusted for age, gender and calendar year of diagnosis	2.61 (2.04, 3.33)	<.001
Model C		
Adjusted for use of rituximab and standard IPI score	1.23 (0.93, 1.64)	0.146
Model D		
Adjusted for gender, calendar year of diagnosis, use of rituximab and standard (age included) IPI score	1.04 (0.76, 1.41)	0.811
Model E		
Adjusted for age, gender, calendar year of diagnosis, use of rituximab and age-adjusted (age excluded) IPI score	1.46 (1.04, 2.05)	0.030
Model F (N=97)		
Adjusted for gender, calendar year of diagnosis, use of rituximab and standard IPI	1.34 (0.82, 2.20)	0.242

B

	Relative hazards of death	
	RH of HIV+ vs. HIV- (95% CI)	p-value
Model A		
Unadjusted	1.65 (1.26, 2.17)	<.001
Model B		
Adjusted for age, gender and calendar year of diagnosis	2.06 (1.50, 2.82)	<.001
Model C		
Adjusted for use of rituximab and standard IPI score	1.32 (0.97, 1.80)	0.075
Model D		
Adjusted for gender, calendar year of diagnosis, use of rituximab and standard IPI score	1.06 (0.76, 1.48)	0.732
Model E		
Adjusted for age, gender, calendar year of diagnosis, use of rituximab and age-adjusted IPI score	1.41 (0.98, 2.01)	0.063
Model F (N=85)		
Adjusted for gender, calendar year of diagnosis, use of rituximab and standard IPI score	1.30 (0.75, 2.24)	0.355

Table 3. Adjusted HR of death from fitting a Cox regression model in all HD

	Relative hazards of death (Iso-HD only)	
	RH of HIV+ vs. HIV- (95% CI)	p-value
Model A		
Unadjusted	2.57 (1.56, 4.24)	<.001
Model B		
Adjusted for age, gender and calendar year of diagnosis	2.62 (1.49, 4.60)	<.001
Model C		
Adjusted for use of ABVD* and stage of disease	2.46 (1.23, 4.91)	0.011
Model D		
Adjusted for age, gender, calendar year of diagnosis, use of ABVD and stage of disease	2.47 (1.21, 5.02)	0.013
Model E (N=32)		
Adjusted for age, gender, calendar year of diagnosis, use of ABVD and stage of disease	1.99 (0.49, 8.06)	0.333

*doxorubicin/bleomicyn/vinblastine/dacarbazine

Conclusions/Limitations

- A poorer overall survival after a diagnosis of lymphoma was observed in HIV-infected compared to HIV-uninfected individuals in the unadjusted analysis
- A shorter survival of HIV-infected people was confirmed for HD after adjusting for calendar year, age, gender, standard chemotherapy (ABVD), lymphoma stage
- For NHL and DLBCL the association between HIV-status and risk of death was only independent of age and calendar year, suggesting a potential detrimental role on survival of more aggressive disease and different chemotherapy approach in HIV-infected people
- Unmeasured confounding due to difference in life-style or other factors not measured in our study could not be ruled out

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