Impact of cART on Incidence and Prognosis of HIV-1-associated Non-Hodgkin-Lymphoma - European Multi-Cohort Study

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Abstract

Background: We studied the incidence, risk factors and survival of NHL in HIV-infected patients in the era of combination antiretroviral therapy (cART), using the data from a large prospective European multi-cohort study, the Collaboration of Observational HIV Epidemiological Research Europe (COHERE). ***Methods:*** We analyzed data of HIV- infected patients (aged >16 years) who were cART naïve at inclusion and started cART after 1.1.1998. cART was defined as a regimen of at least 3 antiretroviral drugs. Patients developing NHL before and while receiving cART were analyzed separately; primary brain lymphoma (PBL) and systemic NHL patients were included. Incidence rates were calculated and risk factors identified using crude and adjusted Weibull random-effects models. Time varying covariates were used to explore the effects of CD4 cell counts and plasma HIV-1-RNA load over time. Survival was estimated using Kaplan-Meier life-table probabilities, with 95% confidence intervals (95% CI). ***Results:*** We evaluated 56,305 patients from 22 cohort studies across Europe with 212,042 person-years at risk. The incidence for NHL (systemic NHL and PBL) in patients not on cART was 519 (95% CI 448-602) per 100,000 person-years (pys) compared to 229 (95% CI 208-252) per 100,000 pys in those on cART. In multivariable analyses risk factors for NHL were older age and low CD4 cell count nadirs in patients not on cART. When included as time up-dated variables, high plasma HIV-1 RNA loads and low CD4 cell counts emerged as independent risk factors. In multivariable analyses risk factors included low CD4 cell count nadirs, older age, MSM and history of Kaposi Sarcoma for patients on cART. Time up-dated HIV-1 RNA plasma concentration and CD4 cell count were also associated with developing NHL while on cART. 847 NHL patients were included in the survival analysis. Of those, 364 (43%) were cART naïve at NHL diagnosis. After one year 66% (95% CI 63%-70%) of systemic NHL and 54% (95% CI 43%-65%) of PBL patients were alive. In multivariable analysis risk factors for death were diagnosis of PBL, low CD4 cell count nadir and history of injection drug use. ***Conclusions:*** The risk of HIV-related NHL is about halved in patients on cART, and this reduction was mediated by suppression of HIV-1 replication and immune recovery. Two thirds of patients diagnosed with HIV-1-related NHL other than PBL survive for longer than one year after diagnosis. Survival is poorer in patients diagnosed with PBL.

Background

We studied the incidence, risk factors and survival of Non-Hodgkin-Lymphoma (NHL) in HIV-infected patients in the era of combination antiretroviral therapy (cART), using the data from a large prospective European multi-cohort study, the Collaboration of Observational HIV Epidemiological Research Europe.

Methods

We analyzed data of HIV- infected patients (aged >16 years) who were cART naïve at inclusion and started cART after 1.1.1998. cART was defined as a regimen of at least 3 antiretroviral drugs. Patients developing NHL before and while receiving cART were analyzed separately. Incidence rates were calculated and risk factors identified using crude and adjusted Weibull random-effects models. Time varying covariates were used to explore the effects of CD4 cell counts and plasma HIV-1-RNA load over time. Survival was estimated using Kaplan-Meier life-table probabilities, with 95% confidence intervals (95% CI).

Incidence

We evaluated 56,305 patients from 22 cohort studies across Europe with 212,042 person-years at risk. The incidence of NHL (systemic NHL and primary brain lymphoma (PBL)) while not on cART was 519 per 100,000 person-years (174 cases, 33,517 person-years) compared to 229 per 100,000 person-years (409 cases, 178,525 person-years) on cART (rate ratio 0.44, 95% CI 0.37-0.53). Risk factors in patients on cART included history of Kaposi Sarcoma (KS), transmission of HIV through sex between men (MSM) and older age. Suppression of HIV-1 replication and increases in CD4 counts were protective. Similar associations were observed in patients not on cART, see Table 1 below.

	Adjusted hazard ratios (95% CI)	
	Not on cART	On cART
Age at start cART (years)		
16-29	1	1
30-39	0.89 (0.56 to 1.43)	1.90 (1.29 to 2.80)
40-49	1.76 (1.08 to 2.85)	2.28 (1.52 to 3.43)
≥ 50	2.71 (1.60 to 4.58)	3.61 (2.38 to 5.50)
Sex		
Women	1	1
Men	1.13 (0.73 to 1.77)	1.14 (0.86 to 1.52)
Transmission risk group		
Injection-drug use	0.94 (0.55 to 1.62)	1.11 (0.80 to 1.54)
MSM	1.25 (0.82 to 1.90)	1.47 (1.13 to 1.91)
Heterosexual	1	1
Other/unknown	1.42 (0.82 to 2.44)	0.94 (0.64 to 1.39)
CDC clinical stage		
Stage A/B	1	1
Stage C without KS	0.82 (0.48 to 1.42)	0.93 (0.72 to 1.19)
Stage C with KS	1.25 (0.39 to 4.03)	1.80 (1.17 to 2.75)
CD4 count time-updated (cells/μ L)		
< 50	1.25 (0.66 to 2.38)	2.00 (1.41 to 2.85)
50-99	1.96 (1.10 to 3.47)	1.67 (1.18 to 2.35)
100-199	1	1
200-349	0.58 (0.35 to 0.94)	0.60 (0.45 to 0.80)
≥ 350	0.34 (0.20 to 0.56)	0.30 (0.22 to 0.40)
HIV-1 RNA time-updated (copies/mL)		
≥ 500,000	2.38 (1.40 to 4.04)	1.46 (0.92 to 2.30)
100,000-499,999	1.82 (1.23 to 2.69)	1.16 (0.80 to 1.68)
10,000-99,999	1	1
501-9,999	0.99 (0.61 to 1.61)	1.15 (0.81 to 1.64)
≤ 500	-	0.63 (0.47 to 0.86)

Table 1: Risk factors for developing NHL: hazard ratios from multivariable models including time-updated CD4 cell counts and HIV-1 viral loads

Survival

847 NHL patients (systemic NHL and PBL) were included in the survival analysis. Of those, 364 patients (43%) NHL was diagnosed while not on cART. Among patients diagnosed with NHL while on cART, 115 (14%) had received cART for less than 90 days and 368 (43%) for more than 90 days. Survival at one year was 66% (95% CI 63-70%) for systemic NHL (n=763) and 54% (95% CI 43%-65%) for PBL (n=84). Patients developing systemic NHL on cART had an increased risk of death compared to patients who were cART naïve at diagnosis, see Figure 1 below. In multi-variable analysis including both patients with systemic NHL and PBL, risk factors for death were history of cART treatment, diagnosis of PBL, low CD4 cell count nadir and history of injection drug use. Hazard ratios were closely similar in analyses excluding PBL patients.

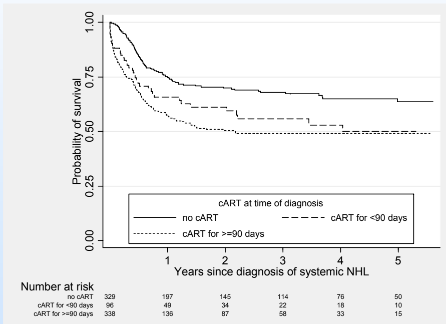

Figure 1: Survival of patients diagnosed with systemic NHL while not on cART, while on cART for less than 90 days or on cART for at least 90 days

Limitations

Main limitations are as follows:

- Incomplete data on CD4 counts
- No data on NHL related information, including histology, tumour load, tumour staging, prognostic markers and chemotherapy received.
- Potential survivor bias: patients who developed NHL while not receiving cART and died before starting cART were not included in the data sets analysed, this may have led to an overestimation of survival in cART naïve patients

Conclusion

The association with Kaposi Sarcoma suggests a role of HHV-8 in HIV-associated NHL, which needs further investigation. Incidence is substantially reduced in patients on cART. Timely initiation of cART is therefore key to the prevention of NHL in the era of cART. Two thirds of patients diagnosed with HIV-related systemic NHL survive for longer than one year after diagnosis. Survival is poorer in patients diagnosed with PBL. More advanced immunodeficiency is the dominant prognostic factor for mortality in patients with HIV-related NHL.

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