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Incidence and risk factors for relapses in HIV-associated non-Hodgkin lymphoma as observed in the German HIV-related lymphoma cohort study

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ABSTRACT

Outcome of HIV-infected patients with AIDS-related lymphomas has improved during recent years. However, data on incidence, risk factors, and outcome of relapses in AIDS-related lymphomas after achieving complete remission are still limited. This prospective observational multicenter study includes HIV-infected patients with biopsy- or cytology-proven malignant lymphomas since 2005. Data on HIV infection and lymphoma characteristics, treatment and outcome were recorded. For this analysis, AIDS-related lymphomas patients in complete remission were analyzed in terms of their relapse-free survival and potential risk factors for relapses. In total, 254 of 399 (63.7%) patients with AIDS-related lymphomas reached a complete remission with their first-line chemotherapy. After a median follow up of 4.6 years, 5-year overall survival of the 254 patients was 87.8% (Standard Error 3.1%). Twenty-nine patients relapsed (11.4%). Several factors were independently associated with a higher relapse rate, including an unclassifiable histology, a stage III or IV according to the Ann Arbor Staging System, no concomitant combined antiretroviral therapy during chemotherapy and R-CHOP-based compared to more intensive chemotherapy regimens in Burkitt lymphomas. In conclusion, complete remission and relapse rates observed in our study are similar to those reported in HIV-negative non-Hodgkin lymphomas. These data provide further evidence for the use of concomitant combined antiretroviral therapy during chemotherapy and a benefit from more intensive chemotherapy regimens in Burkitt lymphomas. Modifications to the chemotherapy regimen appear to have only a limited impact on relapse rate.

Introduction

Over the last two decades, the incidence of AIDS-related lymphomas (ARL) has markedly declined due to the introduction of combination antiretroviral therapy (cART). However, ARL remain a major cause of morbidity and mortality, and represent the highest proportion of all AIDS-related deaths.[1] Patients with ARL are usually treated with the same chemotherapy protocols established in the HIV-negative setting,[2] and the rates of complete remission (CR) achieved are comparable to those reported in their HIV-negative counterparts.[3,4] However, available data on the incidence and potential risk factors of recurrent disease in ARL are scarce, and treatment of disease relapse remains challenging.[4,5] In recent studies on HIV-negative patients with diffuse large B-cell lymphoma (DLBCL), R-CHOP-based regimens (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone) resulted in CR rates of around 65-80%. Differences in response rates largely depend on the pre-treatment International Prognostic Index (IPI) for aggressive lymphomas.[6,7] In patients who had achieved a CR, relapse rates ranged from 6-10%.[6,8] The second most common ARL are Burkitt or Burkitt-like lymphomas (BL).[9,10] In the HIV-negative setting, CR and overall survival (OS) rates of around 80-90% were reported by different groups.[10-12] In a large prospective trial on short-intensive chemotherapy combined with rituximab for patients with BL, the relapse rate was 12%.[10] Although this approach also proved feasible in HIV-related BL,[9] it remains unclear whether relapse rates reported in HIV-negative DLBCL and BL are different to those in ARL. Thus, we investigated the risk factors and incidence of relapse in a large cohort of ARL patients who had achieved a CR after first-line treatment.

Methods

Study design

The German HIV Lymphoma Cohort is an ongoing, prospective observational multicenter study including all adult HIV infected patients who are diagnosed with biopsy- or cytology-proven malignant lymphoma in 33 participating centers since January 2005. Data on HIV-infection and lymphoma characteristics, treatment and outcome are recorded. From the time of lymphoma diagnosis, patients are followed every six months. Ethics approval was obtained from the ethics committees of the University of Cologne (IRC Cologne: 05-174), Germany, and written informed consent was given by each participating patient.

The present analysis includes only patients with aggressive B-cell lymphoma in first CR. Lymphomas were grouped in DLBCL, BL, plasmablastic lymphoma (PBL) and ARL, not further classifiable, the latter group representing aggressive B-cell non-Hodgkin lymphomas (B-NHL) that could not be classified into any subtype. To study the impact of chemotherapy dose intensity on the risk of relapse in patients treated with either R-CHOP-based regimens or the short intensive GMALL protocol,[10] we performed an analysis of dose reductions and delays in chemotherapy cycles. (Information about the GMALL and R-CHOP protocol can be found in the *Online Supplementary Tables S1* and *S2,* respectively). A full-intensity treatment was considered to consist of six cycles of chemotherapy according to the R-CHOP or GMALL protocol administered at 3-week intervals without dose reductions and within a period of 120 days (5x21 days for 6 cycles plus a maximum of 3 days delay per cycle). Less than 6 cycles of chemotherapy were classified as "cycle reduction" and the treatment duration was calculated according to the number of cycles given. If the dose of any chemotherapy drug was reduced by 20% or more, treatment intensity was considered to be reduced.

As positron emission tomography (PET) scans were not routinely performed, the 1999 standardized response criteria for non-Hodgkin's lymphomas[13] were used rather than the 2007 criteria.[14] CR was defined as the disappearance of all disease manifestations for at least three months. This definition also includes uncertain complete remission (CRu) that implied a residual mass of 1.5 cm or smaller that remained unchanged over at least three months.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics software (IBM, Armonk, NY, USA), v.24.0. Univariate statistics were performed using Pearson's χ^2, Fisher's exact one-way Analysis of Variance (ANOVA) with Bonferroni-corrected post-hoc test, or Kruskal-Wallis test depending on data. For the multivariate Cox regression analysis, continuous clinically meaningful breakpoints that showed *P*-values below 0.1 in the univariate analysis were considered. Kaplan-Meier curves were used to illustrate the relapse-free survival (RFS) and overall survival. Differences between subgroups were assessed with the log-rank test. RFS was defined as the period between first diagnosis and any lymphoma relapse according to the STEEP criteria.[15] OS was defined as the period between first diagnosis and death from any cause. All-cause deaths as well as "lost to follow up" were censored. All *P*-values were two-sided. $P<0.05$ was considered statistically significant.

Results

Patients' characteristics and outcome

Numbers and characteristics of patients included in the present analysis are depicted in Figure 1. In total, 254 of 399 (63.7%) patients with high-grade NHL of B-cell origin (classified as ARL) reached a CR with their first-line chemotherapy. Of those, 127 had DLBCL, 91 BL, 29 PBL, and 7 ARL, not further classified. ARL was CD20-negative in 24 of 254 cases (9.5%), among them 22 PBL and 2 DLBCL cases. Among 22 PBL cases with information on Epstein-Barr-Virus (EBV) status, EBV was present in 15 (68%). Overall, 86.2% of patients with $CD20^+$ lymphomas received rituximab. Notably, patients diagnosed before 2010 were less frequently treated with rituximab than those diagnosed from 2010 onwards (79% *vs.* 96%, $P<0.001$). Further, 73% of patients with CD4 cell counts less than 50/µl received rituximab compared to 88% with CD4 counts 50/mL or over ($P=0.096$). Patients' characteristics with respect to treatment outcomes are listed in Table 1. OS of patients who achieved CR with first-line therapy was significantly better than that of patients in other response groups (Figure 2). After a median follow up of 4.6 years, 5-year OS of the entire group of all 262 patients in first CR was 87.1% [standard error (SE) 2.3%] (Figure 3A) with differences between lymphoma subtypes: 87.8% (SE 3.1%) in DLBCL, 87.6% (SE 3.7%) in BL, 79.6% (SE 11.3%) in PBL, and 83.3% (SE 15.2%) in ARL, not further classified ($P=0.994$) (Figure 3B).

Incidence of recurrent disease in ARL

After a median follow up of 4.6 years, a relapse of the ARL had occurred in 29 of 254 patients (11.4%). Relapses were observed in 14 patients with DLBCL (11.0%), 9 with

BL (9.9 %), 3 with PBL (11.5%) and 3 with ARL, not further classified (42.9%), after a median follow up of 5.0, 4.6, 3.5 and 6.0 years, respectively. Isolated central nervous system (CNS) relapses were observed in 3 of 29 patients (DLBCL: n=2; BL: n=1). RFS depicted by Kaplan Meier curves is shown in Figure 3C and D. Five-year RFS (5yRFS) was 88.4% (SE 2.9%) in DLBCL, 88.9% (SE 3.5%) in BL, and 88.6% (SE 6.2%) in PBL. By contrast, 5yRFS was lower in patients with ARL, not further classified [57.1% (SE 18.7%); *P*=0.057) (Figure 3D).

Among patients who achieved CR with first-line R-CHOP-based protocols, 5yRFS was 87.8% (SE 3.1%) and 84.4% (SE 8.3%) in DLBCL and PBL, respectively, as compared to 65.5% (SE 12.6) in BL and 40.0% in ARL, not further classified (SE 21.9%; *P*=0.005) (Figure 3E). No significant differences in 5yRFS between ARL subtypes were observed in patients treated with the GMALL protocol (*P*=0.884) (Figure 3F), although the number of patients with subtypes other than BL was very small in this analysis. Of note, patients with BL who received the GMALL protocol had a significantly better 5yRFS than those receiving R-CHOP-based protocols [94.2% (SE 2.8%) *vs.* 65.5% (SE 12.6%); *P*=0.001].

Risk factors for recurrent disease in ARL

Univariate analysis identified several factors associated with a lower risk for ARL relapse such as a low IPI, stage I or II according to the Ann Arbor Staging System, cART given during chemotherapy, CD4 T-cell counts >200x10^9/L, pathology other than ARL, not further classified, and chemotherapy according to the GMALL-protocol (Table 2). These factors were analyzed in a multivariate Cox proportional hazards model, with backward stepwise elimination based on a Wald statistic with *P*≤0.1.

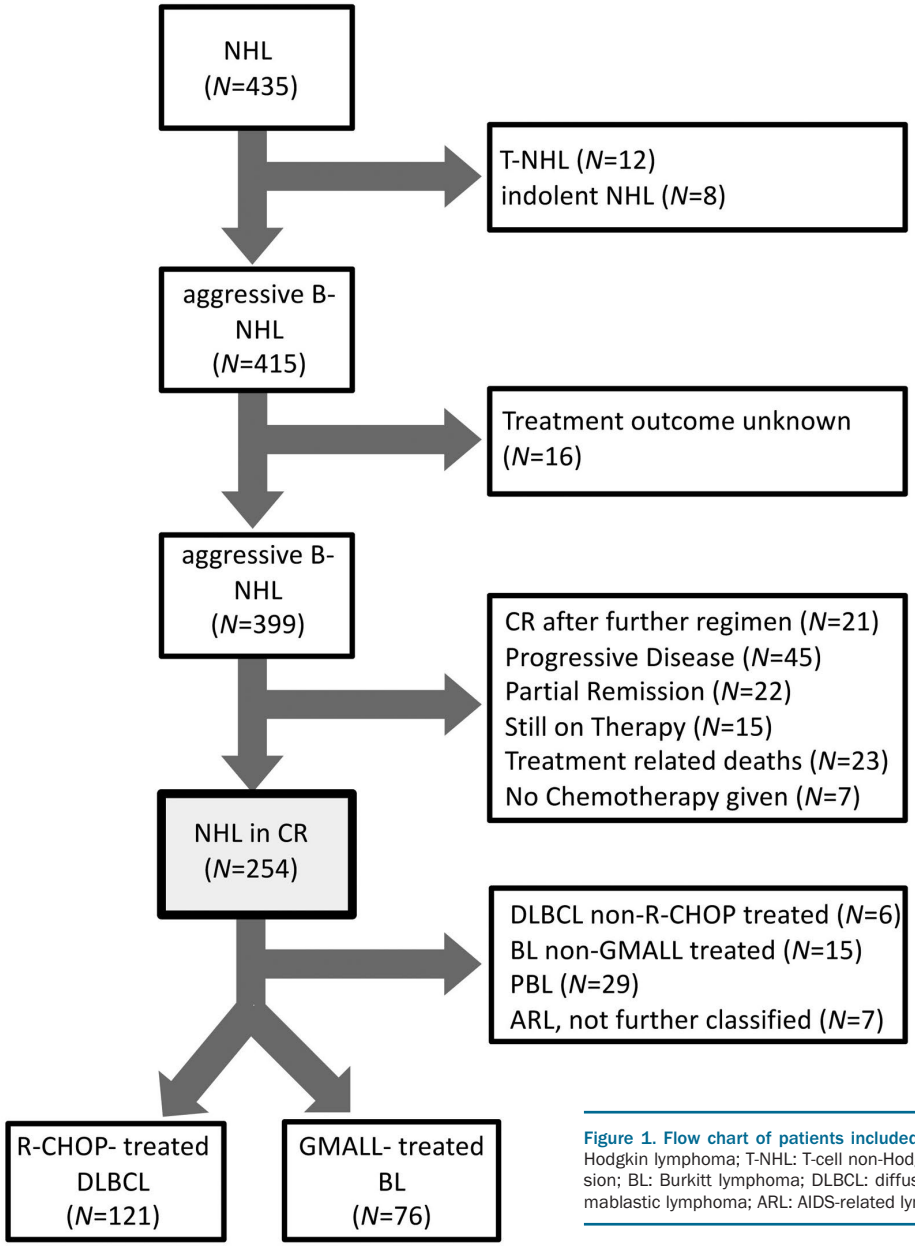

Figure 1. Flow chart of patients included in the present analysis. NHL: non-Hodgkin lymphoma; T-NHL: T-cell non-Hodgkin lymphoma; CR: complete remission; BL: Burkitt lymphoma; DLBCL: diffuse large B-cell lymphoma; PBL: plasmablastic lymphoma; ARL: AIDS-related lymphoma.

After two elimination steps, histology [BL: Hazard ratio (HR) 2.60 95% Confidence Interval (95%CI): 0.92 – 7.4, PBL: HR 1.28 95% CI 0.36-4.57, ARL, not further classified: HR 5.08 95% CI 1.13 – 22.90, indicator = DLBCL), stage III or IV according to the Ann Arbor Staging System (HR 4.85 95%CI 1.44 – 16.34), no concomitant cART (HR 4.28 95%CI 1.19 – 15.39) and use of R-CHOP (HR: 7.59 95%CI 1.87 – 30.81) remained in the model (Table 2). A higher IPI was no longer predictive anymore in the multivariate model.

Dose intensity of chemotherapy

Since chemotherapy regimen (R-CHOP or GMALL) seems to be critical for RFS, we investigated how many patients of all aggressive B-NHL had any kind of reduction (either in the number of chemotherapy cycles or in the treatment intensity) or a delay during their treatment. Results of dose intensity analysis are shown in *Online Supplementary Table S3*. Overall, 32.7% of the patients had a treatment delay, 13.8% had dose reductions, and 16.5% had reduced numbers of chemotherapy cycles

Table 1. Patients' characteristics based on their treatment outcome.

	CR after first-line chemotherapy (n=254)	CR after further lines chemotherapy (n=21)	Progressive disease (n=45)	Partial remission (n=22)	On chemotherapy (n=15)	Treatment related deaths (n=23)	No chemotherapy given (n=7)	Total (N=387)	P
Median age (years)	44	48	45	44	50	48	46	45	0.104[b]
Male	230 (91%)	20 (95%)	44 (98%)	21 (96%)	15 (100%)	21 (91%)	6 (86%)	357 (92%)	0.514[a]
Median viral load (copies/mL)	19031	26790	40208	7159	11387	2390	105000	18557	0.784[b]
HIV-RNA below limit of detection	74 (30%)	5 (24%)	11 (25%)	8 ((36%)	4 (29%)	8 (35%)	2 (29%)	112 (30%)	0.903[a]
Median $CD4^+$ T cells ($x10^6/L$)	248	190	111	186	153	157	58	212	0.006[b]
$CD20^+$ lymphoma	213 (90%)	20 (95%)	34 (81%)	18 (90%)	10 (83%)	13 (68%)	4 (67%)	312 (87%)	0.044[a]
BM involvement	47 (20%)	7 (33%)	15 (39%)	6 (29%)	3 (21%)	6 (21%)	1(17%)	85 (23%)	0.190[a]
CNS involvement	17 (8%)	2 (10%)	8 (21%)	2 (11%)	1 (9%)	5 (33%)	0 (0%)	36 (11%)	0.023
IPI score									
Low	100 (42%)	5 (24%)	8 (18%)	2 (11%)	5 (39%)	2 (9%)	0 (0%)	122 (36%)	
Intermediate	104 (44%)	11 (52%)	20 (46%)	13 (68%)	6 (42%)	11 (50%)	3 (43%)	168 (46%)	
High	34 (14%)	5 (24%)	16 (36%)	4 (21%)	2 (15%)	9 (41%)	4 (57%)	74 (20%)	<0.001[a]
Lymphoma subtype									
DLBCL	127 (50%)	7 (33%)	24 (53%)	13 (59%)	7 (47%)	7 (30%)	4 (57%)	189 (49%)	
BL	91 (36%)	11 (52%)	12 (27%)	5 (23%)	4 (27%)	9 (39%)	1 (14%)	133 (34%)	
PBL	29 (11%)	3 (14%)	7 (16%)	3 (14%)	3 (20%)	7 (30%)	2 (29%)	54 (14%)	
ARL, not further classifiable	7 (3%)	0 (0%)	2 (4%)	1 (5%)	1 (7%)	0 (0%)	0 (0%)	11 (3%)	0.420[a]
Median follow up (years)	4.64	5.4	0.5	0.7	0.1	0.2	0	2.4	<0.001[b]

BL: Burkitt lymphoma; DLBCL: diffuse large B-cell lymphoma; PBL: plasmablastic lymphoma; IPI: International Prognostic Index; BM: bone marrow; CNS: central nervous system. [a]Two-sided Pearson's χ^2. [b]Kruskal-Wallis test.

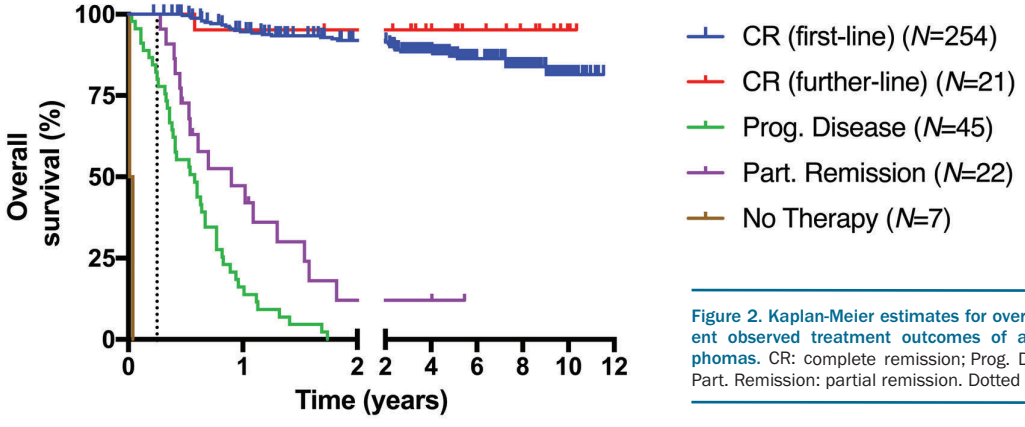

Figure 2. Kaplan-Meier estimates for overall survival (OS) of the different observed treatment outcomes of aggressive non-Hodgkin lymphomas. CR: complete remission; Prog. Disease: progressive disease; Part. Remission: partial remission. Dotted line indicates 3 months.

given. Only 37.0% of patients received their full planned course of therapy.

Patients who experienced treatment delays and/or dose reductions or received a reduced number of chemotherapy cycles were significantly older (42 *vs.* 45 years; *P*=0.042) and had received the GMALL-protocol significantly more often than patients who completed the full planned course of therapy (*P*=<0.001) (*Online Supplementary Table S3*). Overall, 86.2% of patients with CD20$^+$ lymphomas received rituximab. There was no difference in the relapse rate between patients with or without administration of rituximab (*P*=0.75), and our results remained consistent when patients without rituximab were excluded (*data not shown*).

Factors influencing the RFS

To investigate the influence of different factors, including treatment reduction or delay on 5yRFS, we investigat-

Table 2. Risk factors for 5-year relapse-free survival (including all aggressive non-Hodgkin lymphoma in first complete remission; n=254).

		Aggressive NHL (N=254)		
		5-year relapse-free survival %	*P* (univariate)	*P* (multivariate)
Sex	Male (n=230)	87		
	Female (n=24)	96	0.229	
Age	>60Y (n=24)	77		
	<60Y (n=228)	89	0.178	
CNS involvement	Yes (n=17)	82		
	No (n=204)	90	0.305	
BM involvement	Yes (n=47)	81		
	No (n=193)	90	0.101	
Bulky Disease	Yes (n=44)	86		
	No (n=137)	88	0.637	
CD4$^+$ T cells <50x10^9/l	Yes (n=37)	86		
	No (n=202)	88	0.573	
Prior AIDS-defining illness	Yes (n=56)	87		
	No (n=193)	88	0797	
IPI score	Low (n=100)	95		Indicator
	Intermediate (n=104)	84		0.760
	High (n=34)	82	0.039	0.853
Ann Arbor stage	I/II (n=93)	95		
	III/IV (n=156)	83	0.005	0.011
Extranodal involvement	Yes (n=71)	87		
	No (n=181)	88	0.936	
ECOG score	0-1 (n=159)	89		
	2-5 (n=78)	86	0.635	
Elevated LDH	Yes (n=146)	86		
	No (n=96)	92	0.143	
Antiretroviral Treatment	Viral load b.d. (n=74)	88		
	Naive (n=134)	88		
	Therapy failure (n=39)	87	0.986	
cART during Chemotherapy	Yes (n=234)	89		
	No (n=9)	67	0.033	0.026
CD20 positive lymphoma	Positive (n=213)	88		
	Negative (n=24)	87	0.888	
Lymphoma subtype	DLBCL (n=127)	88		Indicator
	BL (n=91)	89		0.072
	PBL (n=29)	89		0.703
	ARL, not further classifiable (n=7)	57	0.064	0.034
Chemotherapy	CHOP (n=163)	84		
	GMALL (n=87)	95	0.013	0.005

Univariate statistics: Log rank test. Multivariate statistics: Cox regression. Viral load b.d.: Viral load below limit of detection; cART: combination antiretroviral therapy; BL: Burkitt lymphoma; DLBCL: diffuse large B-cell lymphoma; PBL: plasmablastic lymphoma; IPI: International Prognostic Index; BM: bone marrow; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group scale.

ed two selected groups: patients with DLBCL receiving R-CHOP-based regimens and patients with BL receiving the GMALL-regimen (see also Figure 1). In patients with DLBCL who received a R-CHOP-based treatment, a high IPI, an elevated LDH, stage III or IV according to the Ann Arbor Staging System, and bone marrow involvement at first diagnosis were associated with a significantly increased risk of relapse (*Online Supplementary Table S4*). However, none of these parameters turned out to be an independent risk factor in the Cox proportional hazards model. Of note, chemotherapy dose reductions, treatment delays or a reduced number of R-CHOP-cycles given did not adversely affect 5yRFS (*Online Supplementary Table S4*).

By univariate analysis, patients with BL who underwent GMALL-chemotherapy had a significantly increased risk of relapse if the following factors were present: diagnosis of another AIDS-defining disease prior to BL diagnosis, CNS-involvement, failure of cART defined as measurable viral loads despite concomitant cART, concomitant cART during chemotherapy, and reduced numbers of chemotherapy cycles administered (*Online Supplementary Table S4*). However, none of these factors remained significant in the Cox proportional hazards model.

Discussion

In this large prospective cohort study of 254 ARL patients who had achieved a CR with first-line chemotherapy (64% of all cases), the total relapse rate was 11% after a median follow up of 4.6 years. Patients with DLBCL who were mainly treated with R-CHOP-based regimens had a relapse rate of 11%. These rates are in line with the 6-10% relapse rates reported in HIV-negative DLBCL in first CR.[6,8] Notably, the 10% relapse rate of patients with BL who were mainly treated with the GMALL protocol compares favorably with the 12% relapse rate reported in the HIV-negative setting.[10]

Outcome of patients with ARL in which histology was not further classifiable was poor with a 5yRFS of only 57%. There was no difference in type and intensity of chemotherapy to that used in DLBCL (*data not shown*), therefore these cases may represent a subgroup of highly aggressive lymphomas that may benefit from intensive chemotherapy regimens.

Even though the overall survival of patients with PBL was shown to be significantly worse than that in DLBCL and BL,[16,17] there was no difference in relapse rates

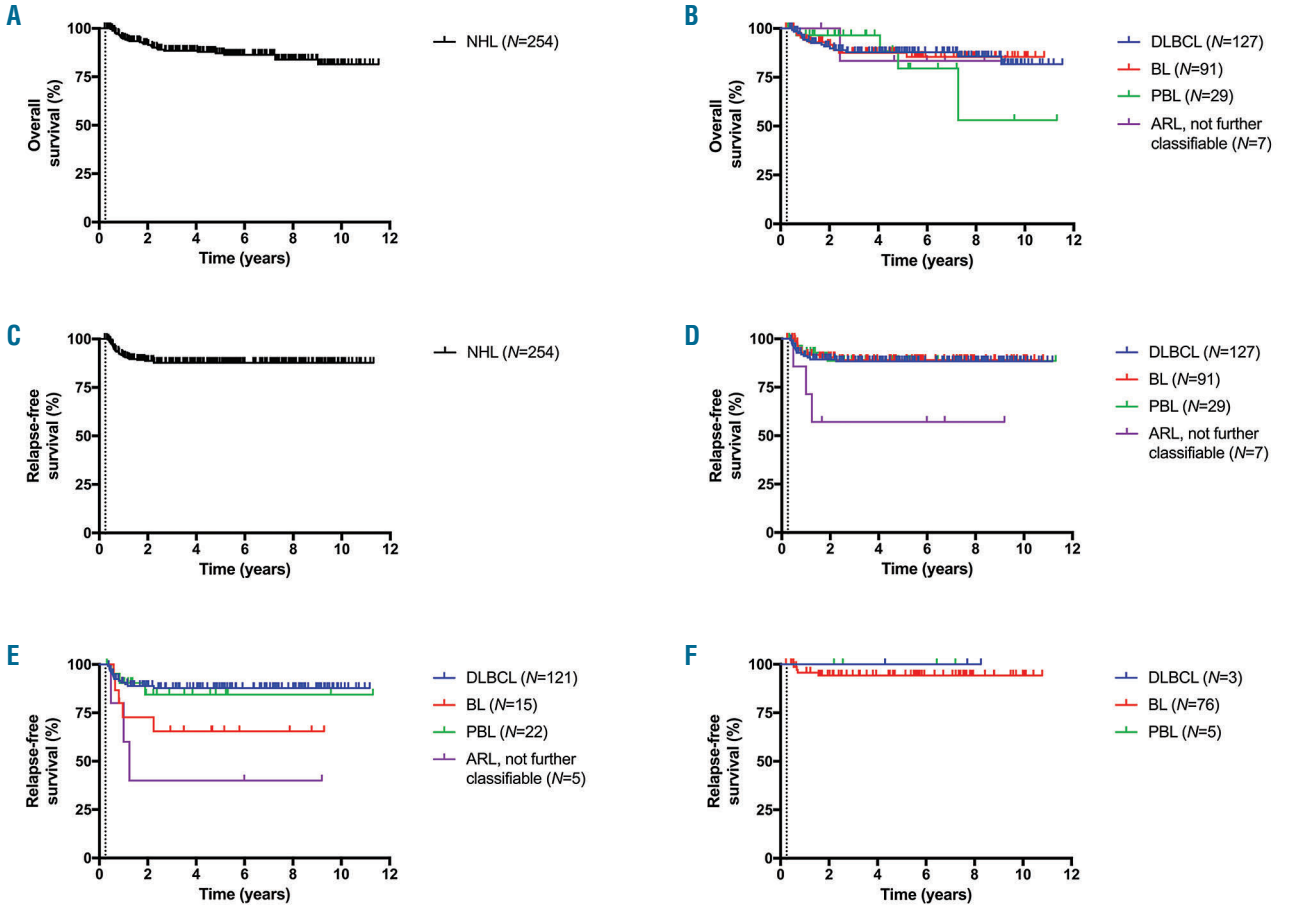

Figure 3. Kaplan-Meier estimates for aggressive non-Hodgkin lymphoma (NHL) that achieved complete remission (CR) after first-line chemotherapy. (A) Overall survival of all AIDS-related lymphomas (ARL) and of (B) different subtypes (Log rank test: P=0.982). (C) Relapse-free survival of all ARL and of (D) different subtypes (P=0.064). (E) Relapse-free survival of different subtypes treated with R-CHOP-based regimens (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone) and (F) GMALL-based chemotherapeutic regimens (P=0.006 and P=0.79, respectively). DLBCL: diffuse-large B-cell lymphoma; BL: Burkitt-lymphoma; PBL: plasmablastic lymphoma. Dotted line indicates 3 months.

between patients who have achieved a CR (12%) to those observed in DLBCL and BL. The inferior OS of the small patient group of PBL may at least in part be explained by 3 late deaths 4-7 years after first diagnosis that were unrelated to lymphoma: one case of sepsis due to pneumonia and 2 cases of secondary malignancies (lung cancer and oral cavity cancer).

AIDS-related lymphoma patients with an intermediate and high IPI had higher relapse rates and a lower 5yRFS than those with a low IPI in univariate analysis. The lack of significance in the multivariate analysis was somewhat surprising as previous studies have demonstrated strong prognostic relevance of the IPI in ARL.[17,18] Whether patients with HIV-related DLBCL and intermediate or high IPI may benefit from more intensive treatments such as the CHOEP regimen, as has been shown in the HIV-negative setting, remains to be seen.[19,20]

Previous studies have shown that concomitant cART was associated with improved CR rates and a trend toward improved OS.[21] Our results also support a concurrent use of cART as it was associated with better 5yRFS. Several cART regimens with a good safety and tolerability profile and low interaction potential are now available, strongly arguing for a simultaneous cART during ARL chemotherapy.[4]

The use of R-CHOP-based regimens showed significantly less treatment delays and reductions, as compared to the GMALL protocol. However, the majority of patients with BL (84%) received chemotherapy according to the GMALL-protocol which resulted in significantly lower relapse rates compared to R-CHOP-based regimens (Figure 3E and F). Notably, treatment delays and a reduced chemotherapy intensity appeared to have no impact on the relapse-rate in GMALL-treated BL, while, at least in the univariate analysis, a reduced number of chemotherapy cycles was associated with lower 5yRFS. Thus, our data indicate that HIV-infected patients with BL should be treated with the planned number of intensive chemotherapy cycles.[3,8] By contrast, reduced relative dose intensity did not negatively impact 5yRFS in patients treated with R-CHOP-based regimens for DLBCL. This finding does not correspond to data reported in HIV-negative DLBCL and warrants further investigation.[22,23]

It is important to note that this analysis focuses on patients in first CR, and that factors that predict RFS were not necessarily associated with initial treatment response.

Our study has several limitations. First, given the uncontrolled design selection biases cannot be ruled out. Second, the analysis of risk factors associated with outcome is more exploratory in nature. Given the relatively low number of patients in some of the selected subgroups, the statistical power of the analysis is limited and does not allow any firm conclusions to be drawn. Notably, data on potential risk factors for lymphoma relapse such as adherence to ART or cumulative viremia between CR and relapse are not available.[24] Nevertheless, if a CR has been reached, the relapse rate was low regardless of whether the CR was achieved with or without dose reduction and whether rituximab was used or not. Fourth, CRs were not generally confirmed by negative positron emission tomography (PET) scans as recommended by current guidelines for HIV-negative lymphomas.[14,25] However, the role of PET-scanning in HIV-lymphoma remains controversial as the rate of false positive results appears to be higher than in the HIV-negative setting.[26,27] Finally, the number of patients with ARL, not further classified, may have been lowered by reference pathology services which, in turn, may have slightly altered our findings.

In conclusion, both CR rates and relapse rates observed in the German HIV-related Lymphoma Cohort Study are similar to those reported in HIV-negative NHL. These data add to the growing body of evidence showing that treatment outcomes compare favorably with those in patients with NHL and no HIV infection.

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