Treatment and prognosis of AIDS-related lymphoma in the era of highly active antiretroviral therapy: findings from the Swiss HIV Cohort Study

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Objective: To assess the characteristics of combination antiretroviral therapy (cART) administered concomitantly with chemotherapy and to establish prognostic determinants of patients with AIDS-related non-Hodgkin's lymphoma.

Methods: The study included 91 patients with AIDS-related non-Hodgkin's lymphoma from the Swiss HIV Cohort Study enrolled between January 1997 and October 2003, excluding lymphomas of the brain. We extracted AIDS-related non-Hodgkin's lymphoma- and HIV-specific variables at the time of lymphoma diagnosis as well as treatment changes over time from charts and from the Swiss HIV Cohort Study database. Cox regression analyses were performed to study predictors of overall and progression-free survival.

Results: During a median follow up of 1.6 years, 57 patients died or progressed. Thirty-five patients stopped chemotherapy prematurely (before the sixth cycle) usually due to disease progression; these patients had a shorter median survival than those who completed six or more cycles (14 versus 28 months). Interruptions of cART decreased from 35% before chemotherapy to 5% during chemotherapy. Factors associated with overall survival were CD4$^+$ T-cell count (<100 cells/μl) (hazard ratio [HR] 2.95 [95% confidence interval (CI) 1.53–5.67], hepatitis C seropositivity (HR 2.39 [95% CI 1.01–5.67]), the international prognostic index score (HR 1.98–3.62 across categories) and Burkitt histological subtypes (HR 2.56 [95% CI 1.13–5.78]).

Conclusions: Interruptions of cART were usually not induced by chemotherapy. The effect of cART interruptions on AIDS-related non-Hodgkin's lymphoma prognosis remains unclear, however, hepatitis C seropositivity emerged as a predictor of death beyond the well-known international prognostic index score and CD4$^+$ T-cell count.

Introduction

Individuals infected with HIV have a 100- to 400-fold increased risk of developing non-Hodgkin's lymphoma (NHL), mainly high-grade B-cell, compared with the general population [1,2]. However, recent cohort analyses have shown that since the broad introduction of combination antiretroviral therapy (cART) in 1996, the incidence of systemic AIDS-related NLH (ARL) has decreased significantly [3–5]. The lower incidence of ARL in the cART era is probably the result of an improved immune status of the treated HIV-infected population [4]. Moreover, a recent registry-linkage study identified, in addition to improved survival, a decrease in high-grade histology and an increase in chemotherapy use in the era of

cART compared with the pre-cART era [6]. The individual patient with ARL therefore benefits from cART through an improved response to chemotherapy [7–11] and through the prevention of additional AIDS-related diseases. Despite these improvements, taking care of patients with ARL often raises the question as to whether cART can be safely maintained alongside chemotherapy.

The aim of our study was to describe the characteristics of patients with ARL and to assess the administration of cART during the course of chemotherapy. In addition, we report on relevant prognostic determinants in patients with ARL enrolled in the Swiss HIV Cohort Study (SHCS).

Methods

The SHCS is an ongoing prospective study that has been enrolling patients with confirmed HIV infection since 1988 from seven tertiary care centres in Switzerland — that is, five University Hospitals (Basel, Bern, Geneva, Lausanne and Zurich) and two large regional Hospitals (Lugano and St. Gallen) — and specialized private practices. SHCS follow-up visits take place biannually and clinical events such as opportunistic diseases, cancers (for example, Kaposi's sarcoma, ARL and cervical cancer) and death are recorded prospectively (www.shcs.ch). The ethical committees of all participating institutions have approved the study protocol of the SHCS.

We used the SHCS database to identify all patients with systemic ARL in the cART era diagnosed between 1st January 1997 and 1st October 2003. HIV-infected patients with primary lymphoma of the brain were excluded. We supplemented data from the SHCS with retrospectively extracted data on chemotherapy from hospital charts for each of the patients enrolled. The date of censoring for this study was 1st July 2004.

For each of the 91 patients enrolled in this study we extracted the following data: demographic information; $CD4^+$ T-cell counts; prior AIDS status; virological outcome; Epstein–Barr virus (EBV) infection (serology); hepatitis B virus (HBV) infection (based on serology and the presence of hepatitis B surface antigen [HBsAg]); and details of current hepatitis C virus (HCV) infection based on HCV serology (HCV antibodies). We registered cART regimes at the time of lymphoma diagnosis and throughout chemotherapy. Characteristics of the ARL included histology subtype [12], presence of bone marrow infiltration, B-symptoms, whether the patient had undergone a splenectomy, the number of extra nodal sites involved, the presence of anaemia, the Ann-Arbour stage, the International Prognostic Index (IPI) score [13] and the Prognostic Index for ARL [14].

Therapies

We registered the type of chemotherapy with the number of cycles and with the type of cART administered at the start of each chemotherapy cycle. We collected information regarding rituximab, granulocyte-colony stimulating factor (G-CSF) and erythropoietin use in relation to chemotherapy.

Patients on cART were classified into subgroups according to their treatment regimen: boosted protease inhibitors (PI); non-boosted PIs; non-nucleoside reverse transcriptase inhibitors (NNRTI); triple nucleoside reverse transcriptase inhibitors (NRTI); or other cART, where cART is defined as a regimen containing at least three antiretroviral drugs (http://aidsinfo.nih.gov/guidelines). Individuals 'not on cART' were subdivided into one of three categories: (i) 'treatment-naive', if they had never received antiretroviral therapies before; (ii) 'start of cART interruption', where the number of interruptions according to chemotherapy cycles were recorded (that is, before initiation or during any cycle later on; the purpose was to determine when interruptions occur according to a certain chemotherapy cycle but not how long they last); or (iii) 'currently on interruption', which includes the number of patients who are not on cART owing to continued interruption over one or several chemotherapy cycles.

Statistical methods

We examined how the frequencies of the above-mentioned 'not on cART' categories changed with chemotherapy progress over ongoing cycles. Because subjects died during follow up, the denominator of the number of patients decreased with each chemotherapy cycle. Similar to life-table analysis, the number of subjects available at the start of a chemotherapy cycle was calculated as the number at the start of the previous cycle minus the number of subjects who died during the cycle. As no patients were lost to follow up, we did not have to adapt the number at risk for censoring. In the same manner we derived the frequency distribution of the number of chemotherapy cycles administered over time.

Because of potential bone marrow toxicity from zidovudine use [15–17], we further studied the number of chemotherapy cycles administered per patient and the presence of anaemia at each chemotherapy cycle as a proxy for bone marrow suppression in patients whose cART regimen either contained or did not contain zidovudine. We firstly fitted a linear model for the effect of zidovudine at baseline against the number of chemotherapy cycles administered per patient, and secondly fitted a generalized estimating equations (GEE) model for the effect of zidovudine on the occurrence of anaemia at each chemotherapy cycle over the entire course of chemotherapy. Furthermore, to assess potential hepatic toxicity associated with HCV seropositivity, we

fitted a GEE model against the hepatic enzyme alanine aminotransferase (ALT) level above the normal range at each chemotherapy cycle.

Kaplan–Meier analyses were first used to study overall survival and progression-free survival, followed by Cox regression models to assess the association of time-fixed baseline covariates with these outcomes. Progression-free survival refers to time from lymphoma diagnosis to the first progression of lymphoma or death.

Complete remission, partial remission and progression were defined according to the World Health Organization (WHO) criteria [18] and were identified through regular CT scans. The date of diagnosis of disease progression was extracted from patient charts and the date of death taken from the SHCS database. The pre-specified ARL-specific predictors for multivariable Cox regression analyses were the original [19,20] and revised IPI score [14], B-symptoms, anaemia and a Burkitt histological subtype (Burkitt and Burkitt-like). HIV-specific predictors were CD4$^+$ T-cell count (≤100 cells/μl versus >100 cells/μl) [14], HIV transmission through intravenous drug use and HCV co-infection. We abstained, however, from performing regression analyses using EBV and HBV covariates due to low test prevalence's and substantial numbers of missing values regarding EBV serology or HBsAg tests. We examined cART use at the time of diagnosis, removing CD4$^+$ T-cell count from the model as it is an intermediate in the causal pathway between cART use and death. We refrained from testing treatment effects as a time-dependent covariate across chemotherapy cycles (for example, interruptions of cART) due to time-dependent confounding [21].

The amount of missing covariate data was no more than 11% with all outcome values complete. To perform efficient multivariable modelling, we used multiple imputations (MI) to deal with missing covariate values using the MICE package available in R [22,23]. Relevant differences between analyses based on MI and analyses based on complete cases (CC) are reported. All analyses were carried out using SAS version 9.1 and R version 2.3.1 [24].

Results

A total of 91 patients with systemic ARL were identified out of 8,051 registered HIV-infected individuals within the SHCS between January 1997 and October 2003 (Table 1). The median age was 44 years and most patients (81.3%) were male. The median baseline CD4$^+$ T-cell count recorded at time of diagnosis was 110 cells/μl for those not presently receiving cART and 138 cells/μl for those receiving cART, with a corresponding viral load of 4.7 and 2.6 log copies/ml, respectively. Of all patients with ARL, 28% had a prior AIDS-defining illness, while 42% and 28% showed positive serology for hepatitis B and C, respectively. Most patients had a diffuse large-cell lymphoma histology subtype.

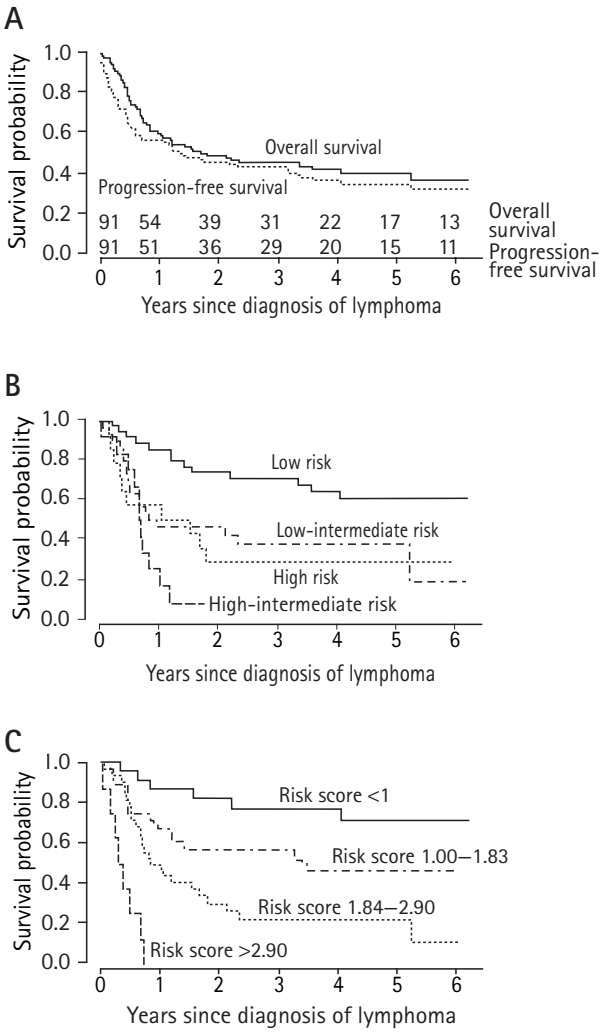
The median follow-up duration was 1.6 years (maximum 7.4 years). The median overall and progression-free survival time was 2.1 and 1.4 years, respectively. Kaplan–Meier estimates for overall and progression-free survival are provided in Figure 1A.

Table 1. Baseline characteristics of 91 patients with AIDS-related lymphoma at time of diagnosis (Swiss HIV Cohort Study, 1997–2004)

Male, *n* (%)	74 (81.3)
Median age, years (IQR)	44 (38.0–54.0)
Median CD4$^+$ T-cell count for patients not receiving cART, cells/μl (IQR)	110.0 (15.0–234.0)
Median CD4$^+$ T-cell count for patients receiving cART, cells/μl (IQR)	138.0 (82.0–271.0)
Patients with CD4$^+$ T-cell count <100 cells/μl, *n* (%)	34 (37.4)
Patients with CD4$^+$ T-cell count ≥100 cells/μl, *n* (%)	57 (62.6)
HIV RNA, log copies/ml	
Not receiving cART, median (IQR)	4.7 (2.9–5.1)
Receiving cART, median (IQR)	2.6 (1.5–4.8)
Prior AIDS, *n* (%)	25 (27.5)
Intravenous drug user, *n* (%)	29 (31.87)
Co-infections	
EBV, *n* (%)*	28 (30.8)
HBV, *n* (%)†	38 (41.8)
HCV, *n* (%)	25 (27.5)
Histology	
Burkitt subtype lymphoma, *n* (%)	11 (12.1)
Diffuse large-cell lymphoma, *n* (%)	72 (79.1)
Follicular lymphoma, *n* (%)	1 (1.11)
Anaplastic large-cell lymphoma, *n* (%)	1 (1.11)
Large-cell plasmoblastic lymphoma, *n* (%)	2 (2.2)
Unclear, *n* (%)	3 (3.3)
International prognostics index score‡	
Low risk 0–1, *n* (%)	29 (31.9)
Low-intermediate risk 2, *n* (%)	26 (28.6)
High-intermediate risk 3, *n* (%)	12 (13.2)
High risk 4, *n* (%)	14 (15.4)
Ann-Arbor stage	
I, *n* (%)	19 (20.9)
II, *n* (%)	18 (19.8)
III, *n* (%)	11 (12.1)
IV, *n* (%)	40 (44.0)
Splenectomy, *n* (%)	4 (4.4)
B-symptoms, *n* (%)	46 (50.6)
Extranodal disease	
Bone marrow infiltration, *n* (%)	12 (13.2)
Number of extra nodes, median (IQR)	1 (1–2)

*Fifty-five patients with missing values on Epstein–Barr virus (EBV) infection. †Forty patients with missing values on HBsAg. ‡Ten patients with missing values on international prognostics index score. HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range.

Figure 1. Kaplan–Meier analyses



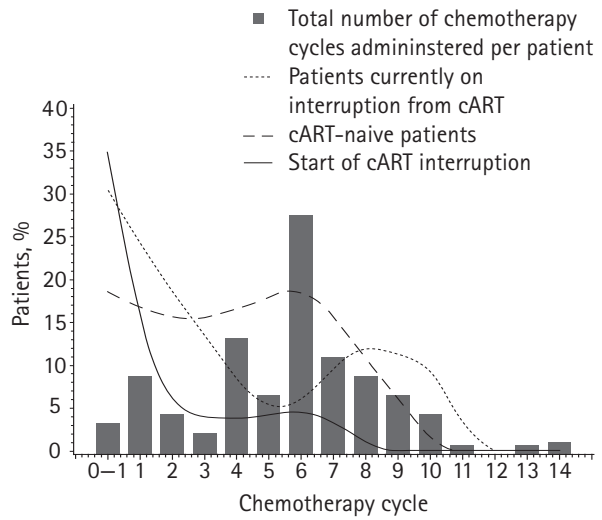
(A) Kaplan–Meier analysis of overall survival and progression-free survival in 91 patients with ARL. Overall survival stratified by (B) the original International Prognostics Index and (C) the Prognostic Index for systemic AIDS-related lymphoma (Swiss HIV Cohort Study, 1997-2004).

Chemo- and antiretroviral therapies

The initial chemotherapy regimen was CHOP (cyclophosphamide, vincristine and prednisone plus at least one anthracyline) in 67/88 patients. Nine patients received CHOP plus rituximab (CHOP-R), 6 patients received rituximab monotherapy (R-mono), and the remainder received a less intensive chemotherapy regimen than CHOP. There were no significant differences between chemotherapy treatment groups regarding overall survival or progression-free survival.

Adding rituximab to chemotherapy became more common after the year 2000 (3/51 versus 12/37 patients; before and after 2000, respectively). The

Figure 2. Changes in combination antiretroviral therapy (cART) in relation to the total number of chemotherapy cycles administered per patient (Swiss HIV Cohort Study, 1997–2004)



distribution of the number of chemotherapy cycles administered per patient over time is shown in Figure 2. On average, 35% of all ARL cases terminated chemotherapy prematurely, that is, received less than six cycles. A quarter of patients (25) received six chemotherapy cycles with the remainder receiving more than six cycles. The single patient who received 14 cycles of chemotherapy initially received six cycles of CHOP, succeeded by four less-intensive chemotherapy cycles before finally receiving four dosages of rituximab monotherapy.

The proportion of patients not receiving cART decreased from 50% at the time of lymphoma diagnosis to 28% over the course of chemotherapy. Non-boosted PIs were the most often administered antiretroviral drugs contributing to almost half of all cART regimens at the end of chemotherapy. Figure 2 illustrates the decreasing number of patients not receiving 'cART' as the number of chemotherapy cycles increased. The majority of treatment interruptions occurred before chemotherapy or during the first cycle. Similarly, in patients who survived and received increasing numbers of chemotherapy cycles, lack of cART because of interruptions became infrequent. Interruption of cART decreased from 35% before chemotherapy to 5% during chemotherapy. The proportion of cART-naive patients remained constantly high at round 20% until the sixth chemotherapy cycle.

In 19 patients zidovudine formed part of the cART regimen at the time of ARL diagnosis, and the effect of this drug on bone marrow suppression was assessed.

Chemotherapy tolerance in terms of the number of chemotherapy cycles delivered per patient was independent of whether zidovudine was added to the cART regimen or not. However, we found a non-significant trend for the development of anaemia with an increasing number of chemotherapy cycles in patients treated with zidovudine. Zidovudine as part of the cART regimen did not significantly affect time to lymphoma progression or death.

We report outcome events occurring before, during and after the course of chemotherapy (Table 2). Three patients died before chemotherapy could be initiated. In total, 44 (48.4%) patients achieved complete remission, while 20 (22.0%) patients reached partial remission during chemotherapy. Disease progression was a frequent reason for premature chemotherapy termination. The number of patients who died early was similar to the number of patients who died later on during chemotherapy but with shorter corresponding median survival times of the former compared with the latter (14 versus 28 months).

Patients seropositive for HCV showed a steadily increasing risk of liver toxicity (ALT levels beyond the normal range) with each chemotherapy cycle administered. The association became statistically significant after the sixth chemotherapy cycle. Nevertheless, the mean number of chemotherapy cycles administered per patient did not differ among HCV-seropositive and HCV-seronegative patients.

Prognosis

We fitted multivariable Cox regression models for both outcomes of overall survival and progression-free survival for all 91 ARL patients. The IPI score, a $CD4^+$ T-cell count <100 cells/μl, hepatitis C seropositivity and Burkitt histological subtype lymphoma were strong, independent predictors for decreased overall survival adjusted for gender, B-symptoms, anaemia, a prior AIDS-defining event and intravenous drug use as the route of HIV transmission. Predictor effects were similar but somewhat smaller for progression-free survival. Also, HCV seropositivity failed to reach statistical significance with progression-free survival (Table 3). When baseline $CD4^+$ T-cell count was replaced with use of cART at baseline, cART had a borderline statistically significant effect on overall survival (hazard ratio [HR] 0.6 [95% confidence interval (CI) 0.3–1.06]; P=0.08) and on progression-free survival (HR 0.62 [95% CI 0.34–1.11]; P=0.10) leaving the other predictors virtually unchanged.

We compared the Prognostic Index for systemic AIDS-related lymphoma (revised IPI score) [14] with the original IPI score. Figure 1 shows Kaplan–Meier curves stratified for the original IPI score (Figure 1B) and the revised IPI score (Figure 1C). Discrimination of prognostic risk groups was better with the revised score where risk categories agreed with the ordering of observed Kaplan–Meier overall survival curves. By contrast, with the original IPI score, the curves corresponding to a 'high risk' and 'high-intermediate risk' crossed each other indicating insufficient discrimination (Figure 1B & 1C). When we exchanged the original IPI score and $CD4^+$ T-cell count with the revised IPI score in the Cox model, leaving the remaining covariates unchanged, we observed larger predictor effects across the revised IPI score categories (HR 2.57–8.93 for overall survival and 1.95–6.1 for progression-free survival) compared with the original IPI score categories. The model fit was similar in both instances.

The analyses based on CC led to the loss of 14 observations. Effect estimates and test statistics from multivariate Cox models were larger based on CC compared with the analyses based on MI data. Because of potentially biased results from the CC analysis, we reported results based on MI [25].

Discussion

Among 91 patients with ARL, 35% stopped chemotherapy prematurely (before completion of the

Table 2. Summary of events during chemotherapy, after termination of chemotherapy and overall in 91 patients with HIV-associated non-Hodgkin's lymphoma (Swiss HIV Cohort Study, 1997–2004)

	Patients per stratum	Complete remission	Partial remission	Progression or death	Death
No chemotherapy, n=91*	3	1	0	3	3
1–5 cycles chemotherapy, n=88*	32	14	9	24	8
≥6 cycles chemotherapy, n=56*	56	29	11	14	9
After completion of chemotherapy†	–	NA	NA	16	33
Total	91	44‡	20§	57¶	53

*Number of patients at the start of the chemotherapy cycle. †Event recorded 1 month after the start of the last chemotherapy cycle. ‡Of the 44 patients who reached complete remission, 3 had a progression but did not die whilst 8 had a progression and died. §Of the 20 patients who reached partial remission, 1 had a progression but did not die whilst 17 had a progression and died. Five patients recorded as reaching a partial remission were also recorded as reaching a complete remission. ¶Four patients with progression were still alive at the end of follow up. NA, not applicable.

Table 3. Multivariable Cox regression analysis for overall survival and progression-free survival in 88 patients treated with chemotherapy (Swiss HIV Cohort Study, 1997–2004)

Predictor	Hazard ratio (95% confidence interval)*	
	Overall survival	Progression-free survival
International Prognostic Index score		
0–1	1 (reference)	1 (reference)
2	1.98 (0.82–4.80)	1.87 (0.84–4.18)
3	3.45 (1.21–9.82)	3.00 (1.04–8.70
4–5	3.62 (1.41–9.27)	3.53 (1.44–8.66)
Burkitt-type lymphoma versus other types	2.56 (1.13–5.78)	2.22 (0.97–5.08)
Seropositivity for HCV	2.39 (1.01–5.67)	1.85 (0.77–4.45)
$CD4^+$ T-cell count <100 cells/μl versus >100 cells/μl	2.95 (1.53–5.67)	2.17 (1.19–3.96)

*Adjusted for gender, B-symptoms, anaemia, HIV transmission through intravenous drug use and prior AIDS. HCV, hepatitis C virus.

sixth cycle) usually owing to disease progression. The median survival time was therefore about half as long in this group compared with patients who completed at least six chemotherapy cycles. Interruption or delayed initiation of cART before or during the first chemotherapy cycle was common practice in the seven tertiary care hospitals participating in the SHCS. Thereafter, in the majority of patients, cART was either maintained, *de novo* initiated or re-initiated. The original IPI score [19] and $CD4^+$ T-cell counts are important predictors of survival and their integration into the revised IPI score for systemic ARL leads to improved risk discrimination. In addition to these known predictors, we identified HCV seropositivity as an independent risk predictor of overall survival in patients with ARL.

There is a large body of direct and indirect evidence supporting the benefit of cART in ARL patients. Numerous studies have reported decreasing incidences of ARL since the advent of cART [26] or the association of either the response to cART [8,10,26,27] or $CD4^+$ T-cell counts >100 cells/μl with increased survival [14]. Despite these well-known benefits of cART, and despite reports on well-tolerated concurrent treatments of cART and chemotherapy [26,28], physicians often hesitate to administer cART and chemotherapy concurrently. One focus of our analysis was therefore the timing of cART during chemotherapy. cART was predominantly interrupted before or during the first chemotherapy cycle. Thereafter, interruptions occurred in <5% of all cases remaining at risk. The high interruption rate prior to the initiation of chemotherapy together with the low interruption rate during chemotherapy suggest that concerns of cumulative toxicity might have been more important in the decision whether or not to withhold or interrupt cART than toxicity itself.

The proportion of patients currently not on cART due to interruption decreased to 5% at the time of the fifth cycle. The subsequent increase (Figure 2) was subject to a smaller denominator, because subjects died during follow up. cART-naive individuals were constantly prevalent at 15–20% up to the sixth chemotherapy cycle. Thereafter, all so-far treatment-naive patients became *de novo* treated. Overall, at the end of chemotherapy the majority of patients were treated with either boosted or non-boosted PI-based cART. However, the increasing prevalence of cART use during the course of chemotherapy should be seen in light of patient selection, as those who survive longer might generally be in better health.

In line with reported bone marrow suppression of zidovudine [15–17], we observed a trend towards an increase of anaemia in patients treated with zidovudine over the course of chemotherapy. Nevertheless, the prevalence of anaemia was low and the effect did not become statistically significant. Moreover, patients on zidovudine-containing cART tolerated an equal number of chemotherapy cycles compared with patients on cART without zidovudine.

In Switzerland, ARL patients are not treated according to chemotherapy treatment protocols but rather in the same way as HIV-negative NHL patients.

Overall, 35% of patients stopped chemotherapy prematurely and we observed an unfavourable median survival in this subgroup. It should be noted that advanced disease stages most likely led to premature chemotherapy termination and unfavourable survival, rather than premature chemotherapy termination as a result of a poor outcome in itself.

The median survival in our cohort was 17 months, which is similar to the experience of other cohorts of ARL patients in the cART era [10,11,29–31] or to patients with advanced high-grade NHL. In agreement with other studies, the majority of patients in this

cohort (79%) had a diffuse large-cell lymphoma (DLCL) subtype [32].

The original IPI score [19] has been confirmed as a useful risk predictor in persons with ARL in several studies [14,32–34]. Similar to Miralles *et al.* [32], IPI scoring did not sufficiently discriminate between the 'intermediate-high risk' and the 'high risk' categories for overall survival. $CD4^+$ T-cell count (≤100 cells/μl versus >100 cells/μl) was a strong independent predictor [14,35] with a hazard of death that was 2.95 times higher in patients with a low $CD4^+$ T-cell count compared to patients with a $CD4^+$ T-cell count >100 cells/μl. As $CD4^+$ T-cell count is an intermediate in the causal pathway between cART use and overall survival or progression-free survival, we exchanged $CD4^+$ T-cell count with cART use at baseline and found that cART had somewhat smaller predictive power. As expected, inclusion of $CD4^+$ T-cell count ≤100 cells/μl into the original IPI score to generate the revised IPI score [14] resulted in better discrimination of the 'intermediate-high risk' and 'high risk' categories (Figures 1B & 1C).

Burkitt and Burkitt-like lymphomas are reputedly more aggressive, with a worse prognosis than the DLCL histological subtype in which prognosis has improved in the HAART era [36–38]. In line with these findings, the risk of death or lymphoma progression was substantially increased in patients with a Burkitt histological subtype in our study population and, in contrast to the conclusion reached by Miralles *et al.* [32], DLCL was not indicative for a poor prognosis.

Because of a potential role of HCV infection in NHL development [2,39], we studied the prognostic impact of HCV seropositivity. HCV seropositivity was an independent predictor for all-cause death beyond the impact of the original IPI score or the Burkitt histological subtype. In particular, this HCV effect is adjusted for the potential confounding effect of intravenous drug use. We further found an interaction effect of HCV seropositivity with the number of chemotherapy cycles administered regarding the occurrence of hepatoxicity. Despite the low prevalence of hepatoxicity, the association became significant after the sixth chemotherapy cycle and in a larger study the effect could have reached statistical significance at a much earlier stage. Although chemotherapy tolerance in terms of numbers of cycles administered did not depend on the HCV serology status, it follows that close monitoring and further research on tolerability and long-term outcomes are needed in these patients. The question as to whether ALT increases were due to activation of HCV or treatment-related toxicity could not be answered, however.

This study has several limitations. Because of the retrospective design, we had no information on the reasons for the interruption or delay of cART or chemotherapy. As mentioned above, our data did not allow further analyses of the effect of cART interruption or premature chemotherapy termination in a time-dependent manner. For such analyses, a causal modelling approach is needed with time-dependent adjustment for disease severity. We also lack information on dosage of administered chemotherapy. Future data should be collected in larger prospective studies to inform ARL patients and physicians on the importance of concurrent cART during chemotherapy. Moreover, data on HCV RNA were only available for a minority of patients at baseline; therefore, we are unable to attribute the prognostic value found for HCV seropositivity to a certain activity state of hepatitis C.

Conclusions

We can draw three main conclusions from this study. Firstly, even in well-experienced centres, cART interruptions occurred frequently before chemotherapy initiation and were not related to poor tolerability. With increasing chemotherapy duration, nearly all ARL patients were on cART. Secondly, the revised IPI score showed better discrimination of risk in patients with ARL and should be used in preference to the original IPI score. Finally, HCV seropositivity was shown to be an independent predictor of overall survival in patients with ARL and might be related to hepatotoxicity during chemotherapy. Future scoring systems should evaluate the prognostic role of HCV infection in patients with ARL.

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Conflict of interest

The authors declare no conflict of interest.

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