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Central nervous system involvement in AIDS-related lymphomas

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Summary

Central nervous system (CNS) involvement is reportedly more common in acquired immunodeficiency syndrome (AIDS)-related lymphomas (ARL). We describe factors and outcomes associated with CNS involvement at baseline (CNS^B) and relapse (CNS^R) in 886 patients with newly diagnosed ARL. Of 886 patients, 800 received either intrathecal (IT) therapy for CNS^B or IT prophylaxis. CNS^B was found in 13%. CNS^B was not associated with reduced overall survival (OS). There was no difference in the prevalence of CNS^B between the pre-combination antiretroviral therapy (cART) and cART eras. 5.3% of patients experienced CNS^R at a median of 4.2 months after diagnosis (12% if CNS^B; 4% if not). Median OS after CNS^R was 1.6 months. On multivariate analysis, only CNS^B (hazard ratio [HR] 3.68, p=0.005) and complete response to initial therapy (HR 0.14, p<0.0001) were significantly associated with CNS^R. When restricted to patients without CNS^B, IT CNS prophylaxis with 3 versus 1 agent did not significantly impact the risk of CNS^R. Despite IT CNS prophylaxis, 5% of patients experienced

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CNS^R. Our data confirms that CNS^R in ARL occurs early and has a poor outcome. Complete response to initial therapy was associated with a reduced frequency of CNS^R. Although CNS^B conferred an increased risk for CNS^R, it did not impact OS.

Keywords

AIDS; Lymphoma; CNS relapse; Non-Hodgkin lymphoma; AIDS-related lymphoma

Introduction

Non-Hodgkin Lymphoma (NHL) is the most common haematological malignancy found in patients who are positive for the human immunodeficiency virus (HIV)(Patel, *et al* 2008). In patients with HIV, NHL often behaves more aggressively and presents at an advanced stage. (Little and Dunleavy 2013, Little, *et al* 2001) Introduction of combination antiretroviral therapy (cART) in 1996 has enabled prolonged survival of HIV-positive patients, and resulted in a reduced incidence of acquired immunodeficiency syndrome (AIDS)-related lymphoma (ARL) with a shift to more favourable histological subtypes.(Bohlius, *et al* 2009, Dunleavy, *et al* 2010, Little, *et al* 2001) Additionally, cART permitted patients with ARL to be treated more aggressively, thereby allowing significantly improved outcomes.(Barta, *et al* 2015, Gopal, *et al* 2013)

Extranodal involvement in general, and specifically central nervous system (CNS) involvement at baseline is increased in patients with ARL.(Desai, *et al* 1999, Levine 1993, Levine, *et al* 2000) The prevalence of CNS involvement at diagnosis (CNS^B) in HIV-negative patients with aggressive NHL has been well characterized and varies depending on lymphoma subtype: 2-5% for diffuse large B-cell lymphoma (DLBCL) and 25-30% for Burkitt lymphoma (BL).(Bernstein, *et al* 2009, Bunn, *et al* 1976, Hollender, *et al* 2002, Liang, *et al* 1990) Furthermore, CNS relapse (CNS^R) in adequately treated patients is a relatively rare event (2-3.5%). The best-established risk factors for CNS^R include a high International prognostic index (IPI) score, elevated lactate dehydrogenase (LDH), extranodal involvement of ≥2 sites, bone marrow and testicular involvement. For high-risk patients without CNS^B, intrathecal (IT) CNS prophylaxis is often used to prevent CNS^R, although the best prophylactic strategy remains to be defined. Prognosis after CNS relapse is poor with a reported median survival of only a few months.(Bernstein, *et al* 2009)

In HIV-positive patients with NHL, the incidence of CNS involvement has reportedly decreased since the introduction of cART and the CD20-monoclonal antibody rituximab. (Navarro, *et al* 2008, Ribera and Navarro 2008) However, only very limited data is available on CNS^B and factors associated with CNS^R in ARL. The objective of our study was to better define the factors and outcomes associated with CNS^B and CNS^R in patients with ARL.

Methods

We used an existing database of 1546 patients with newly diagnosed ARL Patients with primary CNS lymphoma were excluded. Details regarding creation of the database have been described elsewhere.(Barta, *et al* 2013) All patients had been enrolled on phase II or III

prospective clinical trials between 1 January1990 and 31 October 2010. Only patients with complete information on CNS involvement (present vs. absent) at baseline and time of relapse were included in this analysis (n=886). CNS relapse (CNS^R) was defined as new evidence of CNS involvement at any time after initial treatment was completed.

In addition to the presence or absence of CNS involvement at baseline and time of relapse we collected the following patient-, lymphoma-, HIV- and treatment-related variables: age, sex, LDH, age-adjusted IPI (aaIPI), extranodal involvement ≥2 sites, histology [DLBCL, BL, Burkitt-like lymphoma (BLL), or "other"], baseline CD4 count and HIV viral load, concurrent use of cART with initial chemotherapy, prior history of AIDS, use of rituximab during first-line treatment, type of first-line chemotherapy regimen, and type of IT CNS prophylaxis [single agent (methotrexate or cytarabine) versus triple IT therapy (methotrexate, cytarabine, dexamethasone)]. Initial chemotherapy was grouped into bolus, infusional, dose intense and less intense regimens. Bolus regimens include CHOP [cyclophosphamide, doxorubicin, vincristine and prednisone]; infusional regimens included EPOCH [infusional etoposide, vincristine, doxorubicin, oral prednisone, intravenous (IV) cyclophosphamide] and CDE [infusional cyclophosphamide, dexamethasone and etoposide]; dose intense regimens included GMALL (German Multicentre Study Group for the Treatment of Adult Acute Lymphoblastic Leukaemia) and "Burkimab" protocols [prophase of cyclophosphamide and prednisone, followed by multiple cycles using ifosfamide, high-dose methotrexate, cytarabine, teniposide, vincristine, daunorubicin, vindesine, and etoposide (GMALL) +/− rituximab ("Burkimab")], LAL3/97 [alternating combinations of cytarabine, methotrexate, cyclophosphamide, ifosfamide, doxorubicin, teniposide, vincristine and dexamethasone] and ACVBP [doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisolone]; less intense regimens include low-dose CHOP and VS [vincristine and prednisolone]. We determined survival as time from study enrolment until time of death from any cause (overall survival; OS), or until time of lymphoma progression/relapse or death (progression-free survival; PFS). Patients who were lost to follow up were censored at the time of their last follow-up. Enrolment in the pre-cART era was defined as enrolment before 1996; enrolment from 1996 onwards, when combination antiretroviral therapy became the standard of care, was defined as the cART era. CNS involvement was determined per report of the principal investigator of each respective trial.

Descriptive statistics were used to summarize patients' characteristics as well as lymphoma and CNS treatment. Appropriate parametric and non-parametric univariate statistical tests were used to examine the association of each lymphoma, HIV and treatment characteristic with CNS^B and CNS^R. The Kaplan-Meier survival curve was used to plot OS with and without CNS^B and a log rank test was applied to compare them. A multivariate Cox proportional hazard model was applied to simultaneously assess associations of baseline characteristics with CNS^R as well as OS. In separate models, LDH replaced aaIPI to avoid colinearity, and in a subgroup analysis for the limited number of patients for whom information on the variable *extranodal sites ≥2* was available, *extranodal sites ≥2* was added. When we assessed the influence of triple agent vs. single agent IT CNS prophylaxis, patients with CNS^B were excluded from the analysis. Assumptions for the Cox proportional hazards models were evaluated and none were found violated. A p-value <0.05 was considered statistically significant; all statistical tests were two-sided. For statistical analysis we used

SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA). For the variable HIV viral load sites, we imputed missing data using multiple imputations because of heavily missing data; p-values were generated using the MIANALYZE procedure in SAS.

Results

Patient characteristics

We identified 886 patients from 9 different trials (Table I).(Dunleavy, *et al* 2010, Dunleavy, *et al* 2013, Galicier, *et al* 2007, Little, *et al* 2003, Mounier, *et al* 2006, Navarro, *et al* 2005, Oriol, *et al* 2005, Ribera, *et al* 2013, Ribera, *et al* 2008, Spina, *et al* 2005, Xicoy, *et al* 2014)

Six patients received no CNS prophylaxis and 49 patients had incomplete information on CNS relapse and were therefore excluded from the CNS^R analysis (Figure 1). All other patients received treatment for baseline CNS involvement or either single or triple agent IT CNS prophylaxis as part of their initial treatment. Table II describes the patient characteristics. Although about two thirds of the patients studied were enrolled in the cART era, only 53% received concurrent antiretroviral therapy during the time of their initial chemotherapy. Twenty-eight per cent had a prior history of an AIDS-defining illness. The most common histology was DLBCL (64%); 32% had either BL or BLL. As per the aaIPI, the majority of patients had intermediate risk disease (64%).

The most commonly used systemic lymphoma regimen was CHOP (36%), followed by dose intense (29%), less intense (19%) and infusional (15%) regimens. One third of patients (31%) received rituximab with their initial lymphoma treatment. Most patients received single agent IT CNS prophylaxis (71%).

CNS^B was present in 111 patients (13%). As expected, BL/BLL subtypes had increased CNS^B compared to DLBCL (27% vs. 6%, $p < 0.001$). For the 47 patients in whom information on initial presentation was available, 74% (n=35) presented with asymptomatic leptomeningeal involvement, while 13% had epidural disease, and 6% (n=3) each had parenchymal lesions or leptomeningeal involvement with cranial nerve deficits, The prevalence of CNS^B for patients receiving initial lymphoma treatment in the pre-cART or the cART era was 13% in both. The majority of patients with CNS^B achieved a complete response (CR) (89% of patients treated for BL/BLL and 56% of patients treated for DLBCL; see Table SI for details).

Factors associated with CNS relapse

Forty-four of 837 patients experienced CNS^R (5.26%), which constituted 13% of all relapses (44/293). Median time to CNS^R was 4.2 months (0.3-19.3). The frequency of relapse did not differ between histologies (DLBCL 5% versus BL/BLL 6%; p=0.39)

On univariate analysis, a lower likelihood of CNS^R was associated with rituximab use (Odds ratio [OR] 0.23; 95% confidence interval [CI] 0.08-0.65; p=0.006), absence of CNS^B (OR 0.36; 95% CI 0.17-0.72; p=0.004) and CR to initial therapy (OR 0.15; 95% CI 0.08-0.29; p<0.001). Other factors, such as aaIPI, triple vs. single agent IT CNS prophylaxis, and concurrent cART therapy, were not associated with CNS^R. However, on multivariate

analysis (Table III) only CNS^B (Hazard ratio [HR] 3.68; 95% CI 1.49-9.10; p=0.005) and CR to initial therapy (HR 0.14; 95% CI 0.07-0.32; p<0.0001) remained significantly associated with CNS^R. LDH alone (p=0.69) and involved extranodal sites >1 (p=0.70) were also not associated with CNS^R in separate multivariate models. When the analysis was restricted to patients treated in the cART era, only CR with initial treatment remained statistically associated with CNS^R (HR 0.11; 95% CI 0.03-0.42; p=0.001; Table SII). The two-year PFS for patients with CNS^B was 50% and 67% for patients with DLBCL and BLL/BL respectively (Table SI).

Overall survival

CNS^B did not significantly correlate with OS (HR 0.85, 95%CI 0.61 – 1.18; p = 0.59; Figure 2), while rituximab use (HR 0.50, 95% CI 0.34 – 0.73; p= 0.004), infusional chemotherapy (HR 0.72 95%CI 0.54-0.97, p < 0.001), concurrent cART (HR 0.57, CI 0.38 to 0.85; p= 0.005), and lower aaIPI scores (compared to high risk, HR 0.56 for intermediate and 0.27 for low risk; p < 0.0001) were independently associated with increased OS for all patients on multivariate analysis (Table SIII). Median OS for patients with CNS^R was 1.6 months (0-86.4; Figure 3), with only 2 long-term survivors.

Discussion

In our analysis, the rate of CNS^B and CNS^R were similar to those reported for HIV-negative patients with DLBCL or BL.(Bernstein, *et al* 2009, Boehme, *et al* 2007, Cheah, *et al* 2014, Haioun, *et al* 2000, Hoelzer, *et al* 2014) CNS relapses occurred early and prognosis was poor. In the Southwestern Oncology Group trial (SWOG8516), the largest study describing the natural history of CNS^R in patients with aggressive NHL, CNS^R occurred earlier than systemic relapses with a median onset of within 5.4 months of initial therapy and median survival of only 2.2 months, similarly to what we observed.(Bernstein, *et al* 2009)

Reported risk factors for CNS dissemination of systemic aggressive lymphomas include high LDH, high IPI scores and extranodal involvement at diagnosis.(Boehme, *et al* 2007, Hollender, *et al* 2002) In contrast, our analysis did not show any significant association of the aaIPI, LDH, or number of involved extranodal sites with CNS^R. Only CNS^B and less than a CR to initial therapy were found to be significantly associated with risk of CNS^R.

Rituximab has been proven to be safe and effective in ARL.(Barta, *et al* 2013) While its use during upfront lymphoma treatment has been associated in some studies with a decreased frequency of CNS^R, others have not made the same observation. (Boehme, *et al* 2009, Boehme, *et al* 2007, Feugier, *et al* 2004, Mitrovic, *et al* 2012, Villa, *et al* 2010, Wilson, *et al* 2014) For example, a pooled analysis of 2196 DLBCL patients aged ≤60 years treated on the MabThera International trial (MinT) and 5 other German High-Grade Lymphoma Study Group (GHGLSG) protocols found a reduction of CNS^R for patients with an aaIPI score ≥2 when rituximab was part of the initial lymphoma regimen.(Schmitz, *et al* 2012) We detected a significant decrease in frequency of CNS^R with rituximab, but this was lost in the multifactorial model. This suggests that better disease control with the addition of rituximab rather than rituximab itself might lower the risk of CNS^R.

A decreased frequency of CNS^R in patients receiving cART at lymphoma diagnosis was described in a small retrospective series (0/12 if cART versus 5/35 if no cART) (Navarro, *et al* 2008). We did not find any association of CNS^R with cART use concurrent with chemotherapy. However, CNS^B was a risk factor for later CNS^R. Notably, in the study reported by Navarro *et al* (2008), CNS^B was 25% in those not on cART versus 3.2% in those receiving cART at time of lymphoma diagnosis. We observed no difference in CNS^B in the pre-cART and cART era (13% each). As the current study did not evaluate use of cART at time of lymphoma diagnosis, this may account for the seemingly divergent observations between the studies.

The role of IT CNS chemoprophylaxis in preventing CNS^R is unclear, with conflicting results in multiple trials. While there appears to be no benefit of CNS prophylaxis in low-grade lymphomas, there might be a benefit in the more aggressive subtypes.(Haioun, *et al* 2000, Vitolo, *et al* 2011, Wilson, *et al* 2014) Recent findings by the GHGLSG argue against the utility of IT CNS chemoprophylaxis in patients with aggressive lymphomas.(Boehme, *et al* 2009, Schmitz, *et al* 2012) Given that all patients in our cohort received IT chemoprophylaxis, it was not possible to assess the effect of IT CNS prophylaxis on CNS^R. Nevertheless, the number of agents used for CNS prophylaxis, i.e. single agent versus triple therapy, did not affect CNS^R incidence in our analysis. However, some chemotherapy regimens, particularly those for BL/BLL, included systemic agents known to attain therapeutic CNS drug levels, such as cytarabine and methotrexate. These may be better than IT CNS prophylaxis at preventing CNS^R in high-risk DLBCL.(Abramson, *et al* 2010, Cheah, *et al* 2014)

The short interval between diagnosis and median time of relapse in our study confirms the impressions that CNS^R is most likely secondary to undiagnosed baseline CNS involvement. (Bernstein, *et al* 2009) Underdiagnosis of CNS^B can occur with conventional cytology (CC) as the only test for cerebrospinal fluid (CSF) involvement by malignant lymphocytes. Flow cytometry (FCM) appears more sensitive in detecting occult lymphomatous leptomeningeal involvement than CC alone. Hegde, *et al* (2005) analysed CSF from 51 patients with NHL and high-risk features for CNS dissemination using both FCM and CC. Eleven tested positive by FCM, only 1 by CC. Furthermore, patients who tested positive by FCM had a higher rate of subsequent CNS relapse. Benevolo, *et al* (2012) reported similar results (CSF+ by FCM: 10% vs. 4% by CC alone; HR for CNS^R in FCM+ vs. FCM- patients: 8.16; 95%CI 1.45-46). Of note, in a recent retrospective analysis of patients with DLBCL (n=246), baseline CSF involvement detected by FCM was associated with a higher rate of CNS^R and lower OS (Wilson, *et al* 2014). However, for patients with BL (n=80), the OS was similar between CSF FCM+ and FCM- patients despite a higher rate of CNS^R in CSF FCM+ patients. Nevertheless, in BL patients whose CSF was positive by CC, OS was lower compared to patients whose CSF was negative by CC.(Wilson, *et al* 2014) Most patients in our analysis were tested for CNS^B by CC before the routine use of FCM for CSF testing became established and all received either single or triple agent CNS prophylaxis. Other studies in HIV-negative patients with aggressive NHL found CNS^B to be associated with worse OS.(Benevolo, *et al* 2012, Sancho, *et al* 2010, Wilson, *et al* 2014) In our study, CNS^B was associated with increased CNS^R, but not shortened OS. As expected, and similar to immunocompetent patients, a larger proportion of patients with BL/BLL and CNS^B achieved

a CR with initial therapy and improved survival when compared with DLBCL. This is most probably related to the incorporation of systemic CNS active agents in treatment regimens for BL/BLL compared to DLBCL regimens. However, CNS^R events were uncommon, which could have limited statistical power.

Strengths of our analysis include the large patient number, treatment of all patients as per standard treatment paradigms relevant to the time periods, and accounting for multiple confounding factors. Limitations include the differences in diagnostic technique with which baseline CNS involvement was established, the lack of central pathology review of the lymphoma diagnosis, and the non-uniform use of histological lymphoma classification systems between the included studies, and a selection bias, as only patients treated on clinical trials were included, which could have potentially resulted in underestimation of the poor prognostic impact of CNS^B.

In summary, CNS involvement in systemic ARL is similar to HIV-negative patients. Risk factors for CNS relapse include CNS involvement at diagnosis and achievement of less than a CR with initial therapy. CNS relapses are rare, but occur early in the course indicating possible occult CNS involvement at diagnoses, and generally have poor outcomes. Therefore adequate baseline CNS assessment with CSF flow cytometry at diagnosis is indicated in most patients. No treatment factors in our study were linked to reduced CNS relapses. However, all included patients received either single or triple agent IT CNS prophylaxis. The continued use of IT chemoprophylaxis in an era of better systemic lymphoma control and the optimal prevention strategy for CNS relapses in HIV-infected patients remain to be better defined. Newer agents with CNS penetration would be a welcome addition to front line therapy in high-risk patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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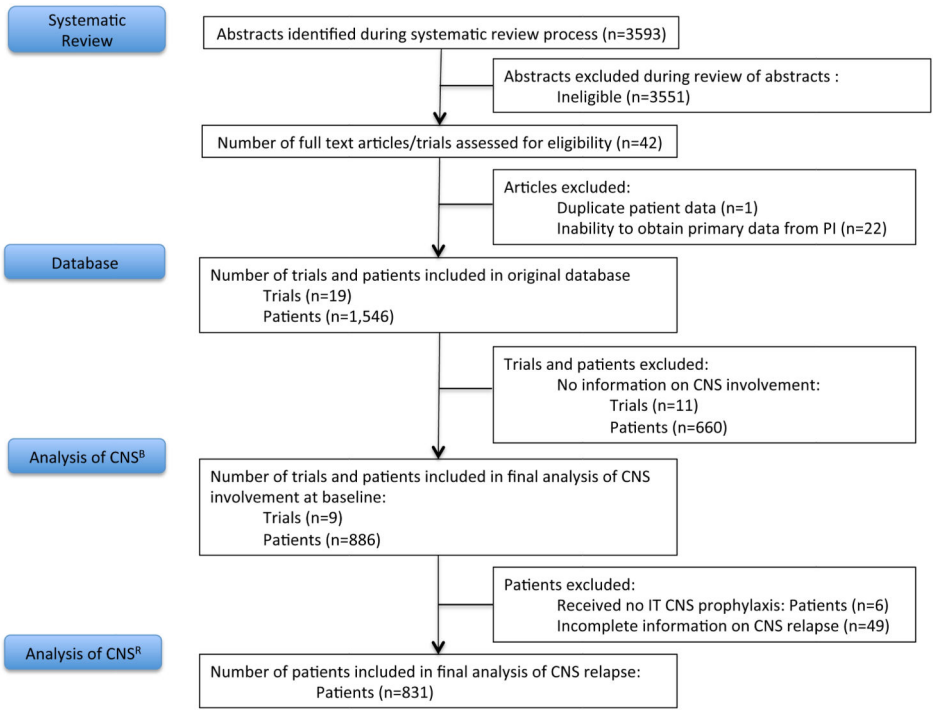

Figure 1.

Consort diagram illustrating the systematic review process and creation of the database CNS, central nervous system; IT, intrathecal; PI, Principal investigator.

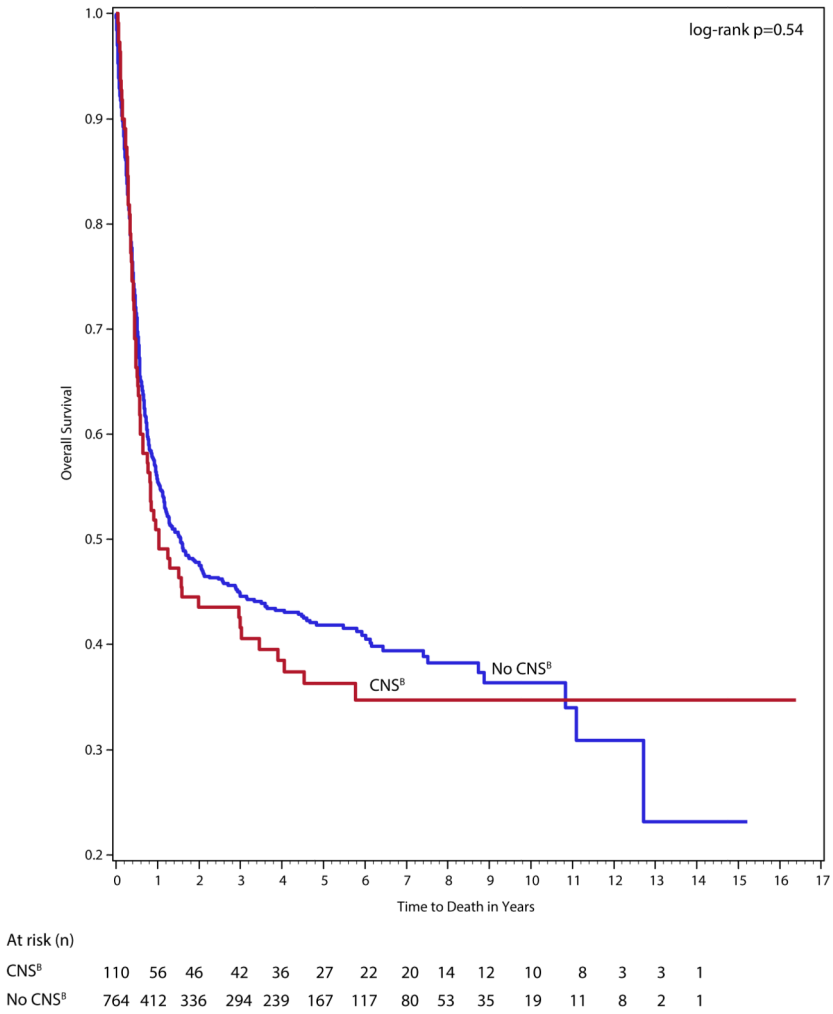

Figure 2.
Survival was not affected by central nervous system involvement at baseline (CNS^B)

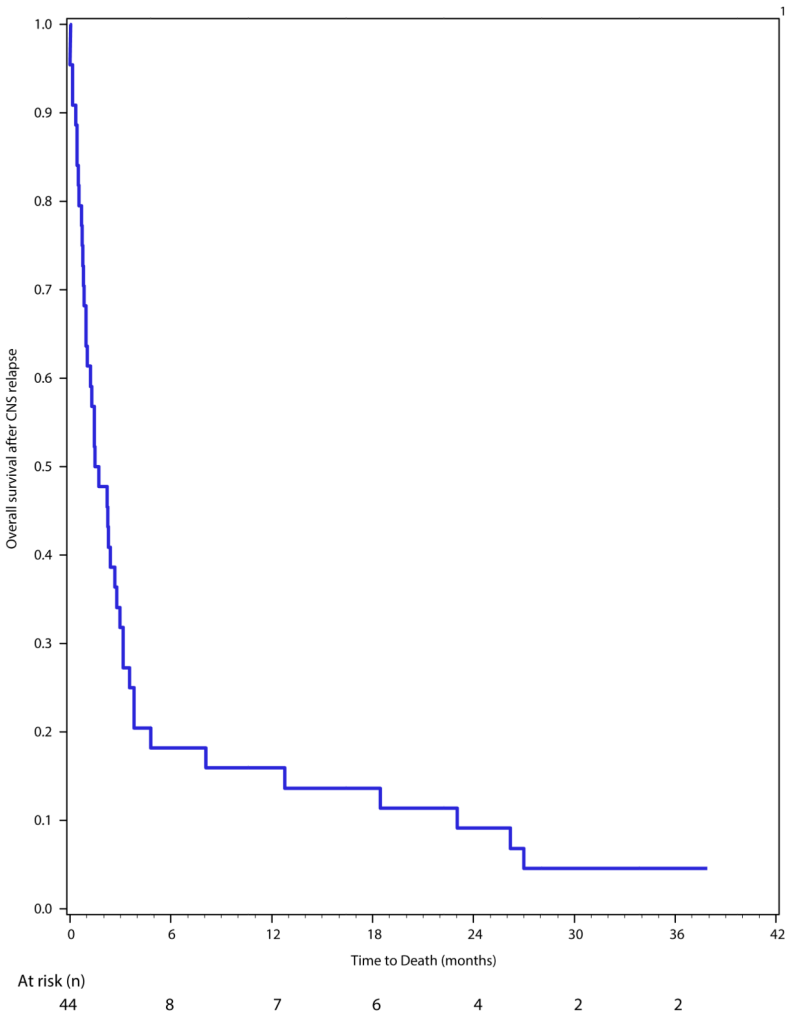

Figure 3.

Overall survival for patients with central nervous system (CNS)relapses. Median survival from time of relapse was 1.6 months

Table I

Characteristics of the 9 trials included in the final pooled analysis.

Reference	Patients (n)	Histology	Chemotherapy regimen used	IV MTX and/or AraC part of initial regimen	Rituximab	Baseline CNS involvement n (%)	Treatment of baseline CNS involvement	Type of CNS prophylaxis	Patients with CNS relapse n (%)
Xicoy *et al* (2014) - Spanish cohort; Ribera *et al* (2013)	40	BL/L3ALL	"Burkimab"/ R-GMALL	yes	yes	3 (7.5%)	TIT twice weekly until clearance of malignant cells in CSF	TIT	1 (2.5%)
Xicoy *et al* (2014) - German cohort	38	BL/L3ALL	"Burkimab"/ R-GMALL	yes	yes	2 (5.3%)	TIT twice weekly until clearance of malignant cells in CSF	TIT	0
Dunleavy *et al* (2010, 2013)	43	BL/DLBCL	EPOCH-RR	no	yes	4 (9.3%)	IT MTX twice weekly until cleared	IT MTX	1 (2.3%)
Ribera *et al* (2008)	81	DBLCL	R-CHOP	no	yes	3 (3.7%)	TIT	TIT	2 (2.5%)
Galicier *et al* (2007)	63	Stage 4 BL/ L3ALL [2]	LMB86 regimen	yes	no	47 (74.6%)	TIT	TIT	n/a[3]
Mounier *et al* (2006)	467	DLBCL/BL/BLL	ACVBP/CHOP/ld-CHOP/VS	no	no	36 (7.7%)	IT MTX twice weekly (maximum x9)	IT MTX	33 (7%)
Navarro *et al* (2005)	49	DLBCL	CHOP	no	no	5 (10.2%)	TIT	IT MTX	3 (6.1%)
Oriol *et al* (2005)	14	BL/L3ALL	LAL3/97	yes	no	3 (21.4%)	TIT	TIT	0
Spina *et al* (2005)	74	DLBCL/BL	R-CDE	no	no	3 (4.1%)	IT MTX or IT AraC	IT MTX (n=68) or IT AraC (n=6)	n/a[†]
Little *et al* (2003)	17	DLBCL/BL/BLL	EPOCH	no	no	5 (29.4%)	IT MTX or IT MTX/ AraC twice weekly until CSF clear, then maintenance	IT MTX : n=6 No ppx: n=6 [1]	4 (23.5%)

AraC, cytarabine; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisolone; BL, Burkitt Lymphoma; BLL: Burkitt like lymphoma; "Burkimab" /R-GMALL ,German Multicentre Study Group for the Treatment of Adult Acute Lymphoblastic Leukaemia protocol consisting of a prophase using cyclophosphamide and prednisone, followed by cycles A, B, and C using rituximab, ifosfamide, high-dose methotrexate, cytarabine, teniposide, vincristine, daunorubicin, vindesine, and etoposide; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CNS, central nervous system; CSF , cerebrospinal fluid; DLBCL, diffuse large B cell lymphoma; EPOCH, infusional etoposide, vincristine and doxorubicin, oral prednisone, intravenous cyclophosphamide; IT, intrathecal; IV, intravenous; ld-CHOP, see m-CHOP; L3ALL, L3 variant of acute lymphoblastic leukaemia; LAL3/97, alternating combinations of cytarabine, methotrexate, cyclophosphamide, ifosfamide, doxorubicin, teniposide, vincristine and dexamethasone; m-CHOP, modified CHOP, dose of cyclophosphamide and doxorubicin reduced by 50% compared with CHOP; MTX, Methotrexate; ppx, Prophylaxis; Remick regimen,

combination of oral lomustine, etoposide, cyclophosphamide, and procarbazine; R-EPOCH, EPOCH concurrently with rituximab; R-CHOP, CHOP concurrently with rituximab; SC EPOCH-RR, short course EPOCH 1 cycle beyond CR to a maximum of 6 cycles, each cycle with 2 doses of rituximab; TIT, Triple intrathecal treatment (methotrexate, cytarabine and dexamethasone); and VS, vincristine and prednisolone; CDE, infusional cyclophosphamide, doxorubicin and etoposide; LMB86 regimen: cytoreductive phase with low-dose cyclophosphamide, vincristine, and steroid therapy (COP), induction phase with 2 cycles of cyclophosphamide, vincristine, prednisone, adriamycin, and high-dose methotrexate (COPADM) and consolidation phase including 2 courses of high-dose cytarabine and etoposide (CYVE) followed by maintenance with 4 courses combining previous drugs with lower dosage; and n/a, not available.

[1] these 6 patients were excluded from the analysis of CNS relapse

[2] defined by either bone marrow or CNS involvement

[3] CNS relapse was set to missing for those who relapsed.

Table II

Characteristics of the patients included in the final analysis (n=886)

Age, years (median, range)	39 (18-74)
Sex, male n (%)	710 (81%)
Enrolment period	
Pre-cART (1990-95) n (%)	279 (31%)
cART era (1996-2010) n(%)	607 (69%)
CD4 count, × 10^9 cells/l (median; range)	0.398 (0-15.84)
Median viral load (copies/ml; range)	27,000 (0-6,080,000)
Prior history of AIDS, n (%)	232 (28%)
Concurrent cART therapy with chemotherapy	449 (53%)
Histology, n (%)	
Diffuse large B-cell lymphoma	570 (64%)
Burkitt/Burkitt-like lymphoma	285 (32%)
Other lymphomas	31 (3%)
Age-adjusted IPI, n (%)[1]	
Low (score=0)	95 (12%)
Intermediate (score 1-2)	488 (63%)
High (score=3)	187 (24%)
CNS involvement at baseline, n (%)	111 (13%)
Type of IT CNS therapy; n (%)	
CNS treatment 2nd to CNS[B]	111 (13%)
Single drug IT chemoprophylaxis	628 (71%)
Triple drug IT chemoprophylaxis	141 (16%)
No IT CNS chemoprophylaxis	6 (7%)
Systemic chemotherapy, n(%)	
CHOP	325 (36%)
Infusional regimens[2]	134 (15%)
Dose intense regimens[3]	261 (29%)
Less intense[4]	166 (19%)
Rituximab use; n(%)	276 (31%)

AIDS, Acquired immunodeficiency syndrome; cART, combination anti-retroviral therapy; IT, intrathecal; IPI, International Prognostic Index; CNS, central nervous system; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone.

[1]Information was not available for all 886 patients

[2]Infusional regimens are EPOCH (infusional etoposide, vincristine and doxorubicin, oral prednisone, intravenous cyclophosphamide), CDE (infusional cyclophosphamide, dexamethasone and etoposide)

[3]Dose-intense regimens are intensive regimens (“Burkimab”/R-GMALL[German Multicentre Study Group for the Treatment of Adult Acute Lymphoblastic Leukaemia protocol: a prophase using cyclophosphamide and prednisone, followed by cycles A, B, and C using rituximab, ifosfamide, high-dose methotrexate, cytarabine, teniposide, vincristine, daunorubicin, vindesine, and etoposide;]) and ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisolone)

[4] Less dose-intense regimens are vincristine/steroids, and low-dose or modified CHOP.

Table III

Multivariate Analysis of risk and treatment factors with development of CNS relapse (CNS^R)

	Hazard Ratio	95% CI	*P*
Age	0.99	0.95 - 1.03	0.72
Gender (Male)	1.10	0.40 – 3.00	0.85
Enrolment Date			0.50
1990-1995	Reference		
1996-2010	0.48	0.06 - 4.11	
CD4 count	1.00	1.00 - 1.00	0.5
Viral load	1.00	1.00 - 1.00	0.09
AIDS history	1.40	0.45 - 4.39	0.56
Concurrent cART Therapy	1.90	0.23 15.97	0.56
Histology			0.07
Diffuse large B-cell lymphoma	Reference		
Burkitt/Burkitt-like lymphoma	2.45	1.14 - 5.31	
Other lymphomas	1.25	0.15 - 10.59	
Age-adjusted IPI			0.77
Low	Reference		
Intermediate	0.96	0.32 - 2.90	
High	0.61	0.12 - 3.03	
CNS^B	3.68	1.49 – 9.10	0.005
No	Reference		
Yes	3.67	1.49 - 9.10	
Treatment[1]			0.71
CHOP	Reference		
Infusional[1]	0.00		
Dose intense[1]	1.15	0.47- 2.80	
Less intense[1]	1.72	0.70 - 4.24	
Rituximab	0.26	0.05 - 1.42	0.12
CR with initial treatment	0.14	0.07 – 0.32	<0.0001

All estimates in the multivariate analysis were adjusted for age, sex, time of enrolment (pre-cART era vs. cART era), CD4 count, viral load, prior history of AIDS, concurrent cART, histology, age-adjusted IPI, CNS involvement at baseline, type of initial chemotherapy, response to initial chemotherapy, and rituximab use.

AIDS, Acquired immunodeficiency syndrome; IPI, International Prognostic Index; cART, combination antiretroviral therapy; CNS, central nervous system; CR, complete response; 95%CI, 95% confidence interval; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone.

[1]Chemotherapy regimens (see Table I for details)