Young high risk patients with diffuse large B-cell lymphoma benefit from dose-dense immunochemotherapy with early systemic CNS prophylaxis

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Abstract

Background: Survival of patients with high-risk diffuse large B-cell lymphoma (DLBCL) is suboptimal, and the risk of central nervous system (CNS) progression is relatively high. We aimed to assess whether a dose-dense immunochemotherapy approach with early systemic CNS prophylaxis improves the outcome and reduces the incidence of CNS events.

Methods: We conducted a phase II trial in patients aged 18–64 years with primary DLBCL and an age-adjusted international prognostic index (aaIPI) 2-3 or site-specific risk factors for CNS recurrence. Treatment consisted of two courses of high-dose methotrexate (HD-Mtx) in combination with biweekly rituximab (R), cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP-14), followed by four courses of R-CHOP-14 with etoposide (R-CHOEP-14) and one course of high dose cytarabine with R (R-HD-AraC). In addition, liposomal cytarabine was administered intrathecally at courses 1, 3 and 5. Our co-primary endpoints were failure- free survival (FFS) and CNS progression rates. The study is registered with ClinicalTrials.gov, number NCT01325194.

Findings: Of 143 enrolled patients, 139 patients were eligible with a median age of 56 years (range 20-64). The majority of the patients had advanced stage, elevated LDH, more than one extranodal site, and B-symptoms. Treatment related death occurred in 5 (3.6%) patients. At five years of median follow-up, FFS, overall survival (OS) and CNS progression rates were 74%, 84% and 2.3%, respectively. Treatment reduced the risk of progression compared to our previous trial, where systemic CNS prophylaxis was given after six courses of biweekly R-CHOEP (HR=0·487; 95% CI 0·308-0·771, p=0·002), and overcame the adverse impact of aaIPI3 and Bcl-2/Myc double hit lymphomas on survival.

Interpretation: The results are encouraging with low toxic death rate, low number of CNS events and favorable survival rates.

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Research in context

Evidence before this study

Before undertaking this study, we considered the fact that there is no clear standard of care for young patients with high risk diffuse large B-cell lymphoma (DLBCL). Besides being at high risk of systemic relapse, this patient population is also at risk for early progression of lymphoma in the central nervous system (CNS). We also searched PubMed with the terms "CNS prophylaxis" AND "diffuse large B-cell lymphoma OR "high-grade lymphoma" for prospective clinical trials up to Dec 2010, and identified six citations that included results from the studies assessing outcomes in response to CNS targeted therapies. None of the publications addressed the impact of systemic CNS prophylaxis specifically for young high-risk patient population in the rituximab era.
In our previous Nordic phase II study conducted between Nov 2004 and Jun 2008, young high risk patients were treated with R-CHOEP-14 regimen followed by systemic CNS prophylaxis with high-dose methotrexate and high dose cytarabine. We observed a CNS relapse rate of 4·5%, which was lower than expected from previous studies. However, all events occurred within six months of diagnosis, suggesting that the patients had a subclinical disease at diagnosis. We designed a study based on the hypothesis that CNS prophylaxis administered in the beginning of the therapy could overcome the subclinical CNS disease, and thus reduce the risk of early clinical CNS progression.

Added value of this study

To our knowledge, this clinical study is the first to prospectively assess the activity and safety of dose-dense immunochemotherapy with early systemic CNS prophylaxis in young patients with aggressive high-risk B-cell lymphoma. We provide evidence that with the regimen used in the present study, most patients, including those with Bcl-2/Myc double hit lymphomas can achieve durable systemic remissions with a low risk of CNS progression.

Implications of all the available evidence

On the basis of these results, the regimen should be considered for a treatment choice of young patients with high risk aggressive B-cell lymphomas. It may also constitute a backbone for new regimens as investigated in combination with novel biological drugs.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is a curable disease with combination chemotherapy. The outcome is variable, but can to some extent be predicted from clinical risk factors included in the IPI score [1,2]. Combination of a CD20 targeted monoclonal antibody, rituximab (R) to CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisolone)-14 or CHOP-21 regimens has substantially improved progression free survival (PFS) and overall survival (OS) in all elderly and young low risk DLBCL patients [3]. However, dose densification of R-CHOP cycles from 21 to 14 days, or infusional dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DA-EPOCH-R) has not provided further survival benefit [4-6].

For young clinically high-risk DLBCL patients the optimal therapy has not been established. Studies comparing conventional doses of chemotherapy with high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) have not convincingly shown an advantage for HDT [7,8], and there is no randomized comparison of the efficacy of adding R to chemotherapy in young, high-risk patients. According to Nordic population-based studies, addition of etoposide (E) to R-CHOP-14 regimen improves OS of young high risk patients [9,10]. R-MegaCHOEP in turn is not superior to R-CHOEP-14 and is associated with significantly more toxicity [11]. Likewise, R-HCVAD/R-MA, a regimen consisting of R with hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with R, high-dose methotrexate (HD-Mtx), and cytarabine did not differ from R-CHOP with respect to survival due to high treatment related mortality [12].

In addition to high risk of systemic relapse, the patients with DLBCL are at risk for progression of their lymphoma in the CNS. In the rituximab era, the rate and patterns of CNS involvement with DLBCL have evolved [13]. The overall risk of CNS progression has reduced to 5%, and for high risk patients with more than one extranodal site and elevated LDH to 10-15% [14-16], and particularly those with renal or adrenal involvement [17]. In addition, localization of CNS relapse has shifted to the brain parenchyma in the majority of cases [13].

No study has demonstrated in a prospective randomized fashion that CNS prophylaxis with intrathecal or systemic Mtx prevents progression of lymphoma in the CNS. German NHL studies have demonstrated that the risk of CNS failure is reduced after addition of E or R to the CHOP regimen [14,18]. Furthermore, some retrospective analyses have shown that HD-Mtx based systemic CNS prophylaxis may reduce the risk of CNS progression [19-21].

The toxicity and efficacy of the R-CHOEP-14 regimen consolidated with late systemic CNS prophylaxis in young high risk LBCL and follicular lymphoma grade 3 patients was investigated in a Nordic NLG-LBC-04 (CRY-04) study [22]. A total of 156 eligible patients with a median age of 54 years at diagnosis (range 20-64) were included. Three-year OS and failure-free survival (FFS) rates were 81% and 65%, respectively. Seven patients experienced CNS progression, all within 6 months of diagnosis. The early appearance of CNS events in the LBC-04 study suggested that the patients had a subclinical disease at diagnosis. We hypothesized that shifting of CNS prophylaxis to the beginning of the therapy could overcome the subclinical disease, and thus reduce the risk of early clinical CNS progression. To address the efficacy and toxicity of early CNS prophylaxis, we initiated the NLG-LBC-05 (CHIC) study, where systemic CNS prophylaxis with HD-Mtx was given in the beginning of therapy, and CNS targeted therapy further intensified by adding intrathecally (i.t)-administered liposomal cytarabine.

Patients and methods

Patients

Eligible patients were 18–64 years old with previously untreated, histologically confirmed CD20+ DLBCL or follicular lymphoma (FL) grade 3B based on the WHO 2008 Lymphoma Classification [23]. Additional details on histology are provided in the Supplement.

Patients had to present WHO performance status <4, without clinical, radiological or cytological signs of CNS involvement with occult cerebrospinal fluid (CSF) involvement (flow cytometry (FCM) + /cytology -) allowed, age-adjusted (aa) IPI 2–3 [1] or site specific risk factors for CNS recurrence defined by more than one extranodal site, testicular lymphoma, stage IIE and higher, paranasal sinus and orbital lymphoma with destruction of bone, or large cell infiltration of the bone marrow, and adequate organ function, allowing the planned treatment schedule. Additional details on inclusion and exclusion criteria, and study procedures are provided in the Supplement.

The protocol was approved by the medical agencies and ethics committees in Finland, Denmark, Norway and Sweden, and the trial registered at ClinicalTrials.gov, number NCT01325194. All patients signed informed consent before study participation.

Treatment

Study design is shown in Figure 1A. Patients were treated with a prephase medication consisting of dexamethasone, R and vincristine, followed by two cycles of HD-Mtx 3 g/m^2, (1·5 g / m^2 to patients 60-64 years) with cyclophosphamide, doxorubicin, vincristine, and prednisone/dexamethasone and R (R-CHOP/R-CHOD) and four cycles of R-CHOP/R-CHOD with etoposide (R-CHOEP/R-CHOED). Dexamethasone was given in conjunction with liposomal cytarabine (Depocyte®) 50 mg i.t. injection at course 1, 3 and 5 (omitted during a period of production halt), otherwise prednisone was given. HD-cytarabine with R was given as a last course and reduced from 12 to 8 g/m^2 for patients aged 60–64 years. Courses were given biweekly with support of pegfilgastrim. Trimethoprim-sulfamethoxazole was used as a prophylaxis for pneumocystis jirovecii pneumonia. Radiotherapy was given at the discretion of the individual centers (30–45 Gy). Indications for giving radiotherapy after the completion of chemotherapy included bulky disease (≥10 cm) at diagnosis, localized PET-positive residual lesions, and residual disease, not eligible for biopsy at a localized site, and potentially curable by radiotherapy.

Statistical analyses

Co-primary end-points were to estimate the proportion of patients that were failure- and CNS progression free at 3 and 1·5 years, respectively. (FFS) was defined as the interval between the registration date and the date of documented progression or lack of response, first relapse, death for any reason or discontinuation/change of therapy because of toxicity, whichever occurred first. CNS recurrence was defined as the interval between registration date and the date of documented CNS progression. Statistical analyses were performed with SPSS v.22.0 (IBM, Armonk, NY, USA). Probability values below 0·05 were considered statistically significant. All comparisons and all comparative tests were two-tailed. Additional details are provided in the Supplement.

Results

Patient demographics

Between March 2011 and December 2014, 143 previously untreated patients, 18 to 64 years of age, were recruited. At central pathology review two cases were excluded as non-DLBCL/non-grade 3B FL. One patient was excluded due to a concomitant CNS lymphoma, one due to concomitant cutaneous follicular lymphoma leaving 139 evaluable patients (Intent to treat population; Figure 1B). The majority of the patients had DLBCL (96%); the other subtypes are specified in Table 1. The patient characteristics were typical for high risk DLBCL with a median age of 56 years (range 20-64), advanced clinical stage, elevated LDH, more than one extranodal site, and B-symptoms (Table 1). A bulky lesion (>10 cm) was present in 37% of the patients, 45% had high CNS-IPI score and 11 CSF samples (8%) were FCM+.

Most patients (n=127, 96%) received the full treatment schedule. I.t liposomal cytarabine was given to 81 (61%) and omitted from the rest of the patients due to a transient production halt. Local radiotherapy was given to 39 (30%) patients, of whom to 25 patients due to a bulky lesion at diagnoses, and to 17 patients due to PET+ lesion at the end of immunochemotherapy.

Biomarker analysis

CD10, BCL6, MUM/IRF4, BCL2, and CD5 positivity was observed in 30%, 83%, 38%, 82%, and 9% of the samples, respectively. On the basis of the Hans algorithm, 54% of the patients were classified as germinal centre B (GCB), and 46% were classified as non-GCB DLBCLs. Among the samples displaying interpretable FISH signals, *BCL2*/18q21, *BCL6*/3q27, and *c-MYC*/8q24 gene rearrangements were found in 27%, 19%, and 14% of the cases, respectively. *BCL2*/18q21 and *c-MYC*/8q24 rearrangements were strongly associated with the GCB subgroup according to the Hans classifier (p=0·001 and p=0·007, respectively). *BCL6*/3q27 rearrangement was not correlated to either category. Double hit lymphomas (DHLs) were found in 9 (12%) of the 77 samples, all within the GCB subgroup.

Toxicity and treatment failures

The fraction of patients with reported grade 3–4 toxic effects, treatment failures due to acute and late toxicities and toxic deaths is shown in Table 2. Thirty-six patients (26%) experienced treatment failure. Of them, 9 were due to acute treatment-related toxicity and 20 due to primary refractory or progressive lymphoma. Four patients developed AML/MDS, one died from lung cancer, and one from unknown reason. Five patients died from treatment-related toxicity.

Responses and survival

Response to therapy is summarized in Supplemental Table S1. Eight patients were not evaluable for response due to toxicity. Of the 119 patients who underwent PET-CT at the end of immunochemotherapy, 91 (77%) achieved a metabolic complete remission (CR), and 19 of 35 patients (21%) with CT-based CRu/partial remission (PR) were in metabolic CR according to PET-CT. Of note, only one out of 15 biopsies (7%) from the PET+ lesions contained viable lymphoma.

After a median follow-up of 60 months, 23 patients had relapsed, three in the CNS (one with intermediate and two with high CNS-IPI score), of whom only one with a pre-therapeutic FCM+ CSF. Twenty-three had died, 16 due to lymphoma (Supplemental Table S1). Five-year FFS, CNS progression, PFS, and OS rates were 74%, 2,3%, 81%, and 84%, respectively (Figure 2A-D). Deauville score 5 at the end of treatment was associated with increased risk of progression and death (Figure 3, Figure S1), whereas other risk factors, such as aaIPI group (0-2 versus 3), number of extranodal sites, and pre-therapeutic FCM+ CSF did not associate with outcome. When the impact of chemotherapy on survival was tested, there was a better PFS and OS rate in patients who were treated with higher total Mtx doses ($\geq 3 g/m^2$; Figure 3). Conversely, PFS and the number of CNS events were not affected by i.t liposomal cytarabine. When the association of biological markers with outcome was examined, none of them correlated significantly with survival (Figure 3).

Outcome for patients treated in NLG-LBC-05 trial compared with the previous NLG-LBC-04 trial

In the NLG-LBC-04 study [22], which served as a preplanned historical control, chemotherapy backbone consisted of R-CHOEP-14 as in the NLG-LBC-05 trial but systemic CNS prophylaxis was given at the end of the immunochemotherapy. In the NLG-LBC-05 trial, the patients had more often more than one EN sites, otherwise patient demographics and response rates were comparable between the two trial cohorts (Supplemental Table S3). However, LBC-05 regimen improved outcome over LBC-04 in terms of better 5-year FFS (74% vs 61%; HR=0·631, 95% CI 0·417-0·955, p=0·030) and PFS (81% vs 65%; HR=0·487, 95% CI 0·308-0·771, p=0·002) (Figure 4A-B). The differences in 5-year OS (84% and 77%; HR=0·684, 95% CI 0·406-1·151, p=0·153) and cumulative incidence rates of CNS recurrence (2·3% and 4·8%, p=0·234) did not reach statistical significance (Figure 4C-D). A favorable impact of the LBC-05 regimen on survival was particularly evident among the patients less than 60 years or with aaIPI3 (Figure 4E and Supplemental Figure S2). In multivariate analysis, which included age, aaIPI, molecular subtype and regimen, aaIPI and regimen remained independent prognostic factors for progression (Supplemental Table S2).

To investigate the impact of early HD-Mtx on the outcome within the biological subgroups, the patients were divided according to their biological subgroup and study cohort.
In the entire study population, dual protein expression (DPE) of BCL2 and c-MYC was the only marker to be significantly correlated with a worse outcome (5-year PFS 77% vs 50%; HR=2·296, 95% CI 1·087-4·851, p=0·029). Neither any single immunohistochemical marker nor the GCB/non-GCB subtype or DHL status significantly affected outcome. However, when treatment interaction in the two Nordic studies was tested, DHL status was associated with a worse PFS and OS after LBC-04 regimen (p=0·011 and p=0·001), as previously reported [24] and now updated at 75 months median follow-up, whereas DHL had no adverse prognostic impact among the patients who received LBC-05 regimen (p=0·99) (Supplemental Figure S2).

Discussion

We present to our knowledge the largest prospective study to date addressing efficacy and toxicity of early systemic CNS prophylaxis and dose-dense immunochemotherapy in patients less than 65 years with high risk aggressive B-cell lymphoma. The aim of this Nordic phase II trial was to

determine if early administration of HD-Mtx based CNS prophylaxis could reduce the incidence of early CNS progressions. Not only was this endpoint achieved, but we could also demonstrate a better systemic control of the disease and superior FFS and PFS rates to our previous LBC-04 study, where systemic CNS prophylaxis was given at the end of the therapy [22]. A relatively low toxic death rate of 3.6% showed that the intensive regimen is feasible for most of the patients. Overall, LBC-05 regimen appeared to be better tolerated than other intensive treatment approaches [6,11,12]. It is plausible that favorable outcome is partially related to lower toxicity, which does not interfere with the therapeutic efficacy.

Since the design and initiation of our trial, a specific model to estimate the risk of CNS recurrence, the CNS-IPI has been established and validated [17]. Some biological risk factors beyond this clinical model have also been described. In particular, DHL and double protein expressor (DPE) lymphomas, and occult CSF involvement (FCM+ / cytology -) have been associated with increased risk of CNS relapse in retrospective series [25-28]. In our study, 45% of the patients were categorized to high risk group according CNS-IPI, with the expected CNS recurrence rate of 10-12% [17]. However, we observed only three CNS events translating to 2·3% CNS recurrence rate in 5 years. As neither the occult CSF involvement nor the DHL entity were associated with the risk of CNS recurrence, we conclude that LBC-05 regimen appears to overcome the adverse prognostic impact of both clinical and biological risk factors.

Given the conflicting evidence-base, lack of prospective randomized studies, and potential toxicity, there is no consensus whether, how, when and to which patient groups CNS prophylaxis should be given. Retrospective analyses have shown that systemic CNS prophylaxis may reduce the risk of CNS relapses [19-21]. In our previous prospective trial for young patients with high risk DLBCL (aaIPI 2-3) [22], a CNS relapse rate of 4·5% was observed. Four of seven relapses were isolated to the brain parenchyma, and all occurred within 6 months after registration, suggesting occult CNS involvement at diagnosis. In the present study, we aimed to reduce CNS relapse rate further without compromising systemic efficacy by combining sensitive FCM based CSF detection analysis with earlier and more intensive systemic and i.t targeted CNS prophylaxis. While shifting of HD-Mtx to the beginning of the therapy translated to significantly improved FFS, PFS and lower number of CNS progressions, i.t administered liposomal cytarabine failed to show additional benefit. This may be related to restricted penetration of i.t therapy to the brain parenchyma, which is the predominant location of CNS recurrence in DLBCL [13,29]. We also analyzed at the impact of Mtx dose, and found a significant quantitative association between the dose and survival. Overall, our results highlight the importance of timing and dose of systemic HD-Mtx administration for optimal outcomes. Low number of CNS relapses appears to be a consequence of a systemic efficacy of HD-Mtx.

We also assessed whether PET positivity (Deauville 4-5) at the end of immunochemotherapy could identify patients, who are unlikely to be cured with NLG-LBC-05 regimen. As expected, we found that majority of the patients (80%) with negative FDG PET scans (Deauville score 1-3) achieved long term remission, and 42% of the patients with Deauville score 5 relapsed. In contrast, the outcome of those with Deauville score 4 was comparable to PET negative patients. Of note was also the finding that only 7% from the PET+ lesions contained viable lymphoma. The observations emphasize the importance of histological confirmation of relapse from PET positive lesions and a possible favorable impact of consolidating radiotherapy.

Our exploratory analyses on clinical variables in the LBC-04 and LBC-05 studies uncovered the influence of age on treatment tolerability and outcomes. While in patients <60 years, the LBC-05 regimen showed clinically meaningful survival benefit over LBC-04 regimen with manageable safety, in patients ≥60 years, toxicity was possibility confounding the therapeutic benefit. In

addition, when the outcome of patients was analyzed according to aaIPI, the benefit of the LBC-05 regimen was particularly seen in the patients with aaIPI3. Based on the data from our prospective trials we propose intensified therapy with early CNS prophylaxis for clinically and biologically high risk patients <60 years, whereas in this setting the regimen should be cautiously considered for the patients ≥60 years.

We were also interested in the impact of the LBC-05 regimen on the outcome of patients with DHL, because several retrospective studies have shown that R-CHOP is not a sufficient therapy for the patients with DHL, and proposed that more intensive Burkitt like regimens, such as DA-EPOCH-R, R-HyperCVAD/MA or R-CODOX-M/IVAC should be used [25,30]. Our subgroup analyses revealed that the patients with DHL status had a similar outcome in response to LBC-05 regimen to all other patients, whereas no such impact could be seen in the previous LBC-04 trial [24]. It thus appears that early administration and/or higher Mtx dose can overcome the adverse prognostic impact of DHL status in aggressive B-cell lymphomas. The exploratory analyses of prognostic variables are limited by relatively small numbers and should be interpreted with caution. The overall conclusion of this and previous studies is that the patients with DHL may benefit from more intensive treatment.

Taken together, we were able to show highly satisfactory PFS, OS and CNS progression rates for the young patients with high risk B-cell lymphoma in response to early HD-Mtx-based CNS prophylaxis followed by dose-dense immunochemotherapy. The LBC-05 regimen was also well tolerated, and should be considered as a treatment choice for patients with young high risk aggressive B-cell lymphomas. Identifying the biologically high risk group and combining the regimen with novel agents seem to be the most logical next steps to further improve the outcome for this high risk patient population.

Authors' contributions

Nordic Lymphoma Group Large B-Cell Lymphoma Working Group (SL, SJ, MJ, MB, JJ, ØF, and HH) designed the protocol. Data management was provided by the Oslo University Hospital Clinical Trial Unit. All authors provided study materials, or enrolled patients to the study, and collected, and assembled data. ER, SS, KB, and M-L.K-L performed pathology reviews. SL, KL, and HH did the primary data analysis and interpretation. All authors contributed to writing of the manuscript, and gave final approval.

Conflict of interest statements

SL reports research funding from Mundipharma and Amgen during the conduct of the study, and honoraria and research funding from Celgene, Roche, Takeda, Bayer and Janssen-Cilag outside the submitted work. JJ reports personal fees from Roche and Gilead outside the submitted work, HH reports research funding from Mundipharma and Amgen during the conduct of the study. The other authors declare no competing interests.

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Role of funding sources

The funders were not involved in interpretation of the data or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Data sharing

Any requests for de-identified trial data and supporting material will be reviewed by the respective trial writing committee in the first instance. Requests that have a methodologically sound proposal will be considered. Proposals should be directed to the corresponding author in the first instance; to gain access, data requestors will need to sign a data access agreement.

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Figure legends

Figure 1. A. Trial profile. B. Patient disposition.

Figure 2. Kaplan-Meier survival estimates for failure free survival (A), progression free survival (B), overall survival (C) and risk of CNS relapse (D).

Figure 3. Forest blot showing subgroup analysis of progression free survival.

Figure 4. Kaplan-Meier survival estimates for failure free survival (A), progression free survival (B), overall survival (C) and risk of CNS relapse (D) according to LBC-04 and LBC-05 trials. Forest blot showing subgroup analysis of progression free survival in LBC-04 vs LBC-05 trials (E). In panel E, progression free survival in case of all patients is adjusted for aaIPI.

Table 1. Patient characteristics

Characteristic	**n=139**	**%**
Age years, median (range)	56 (20-64)	
Male/Female	88/51	63/37
DLBCL NOS	113	81
GCB/Non-GCB/ND	56/47/10	49/42/9
TCRB	5	3·6
PMBCL	8	5·8
Intravascular	1	0·7
FL Grade 3B	5	4·3
Not reviewed	7	5·0
PS ECOG>1	43	31
Stage		
I-II	11	8
III	26	19
IV	102	73
B-symptoms	88	63
LDH⇧	127	91
aaIPI		
0-1*	10	7·2
2	83	60
3	46	33
CNS IPI		
low (0-1 factors)	4	2·9
intermediate (2-3 factors)	72	52
high (≥4 factors)	63	45
Bulky disease	52	37
>1 extranodal sites	81	67
CSF flow +	11	8

*with site specific risk factors for CNS recurrence defined by >1 EN site, testicular lymphoma stage IIE and higher, paranasal sinus and orbital lymphoma with destruction of bone, large cell infiltration of the bone marrow

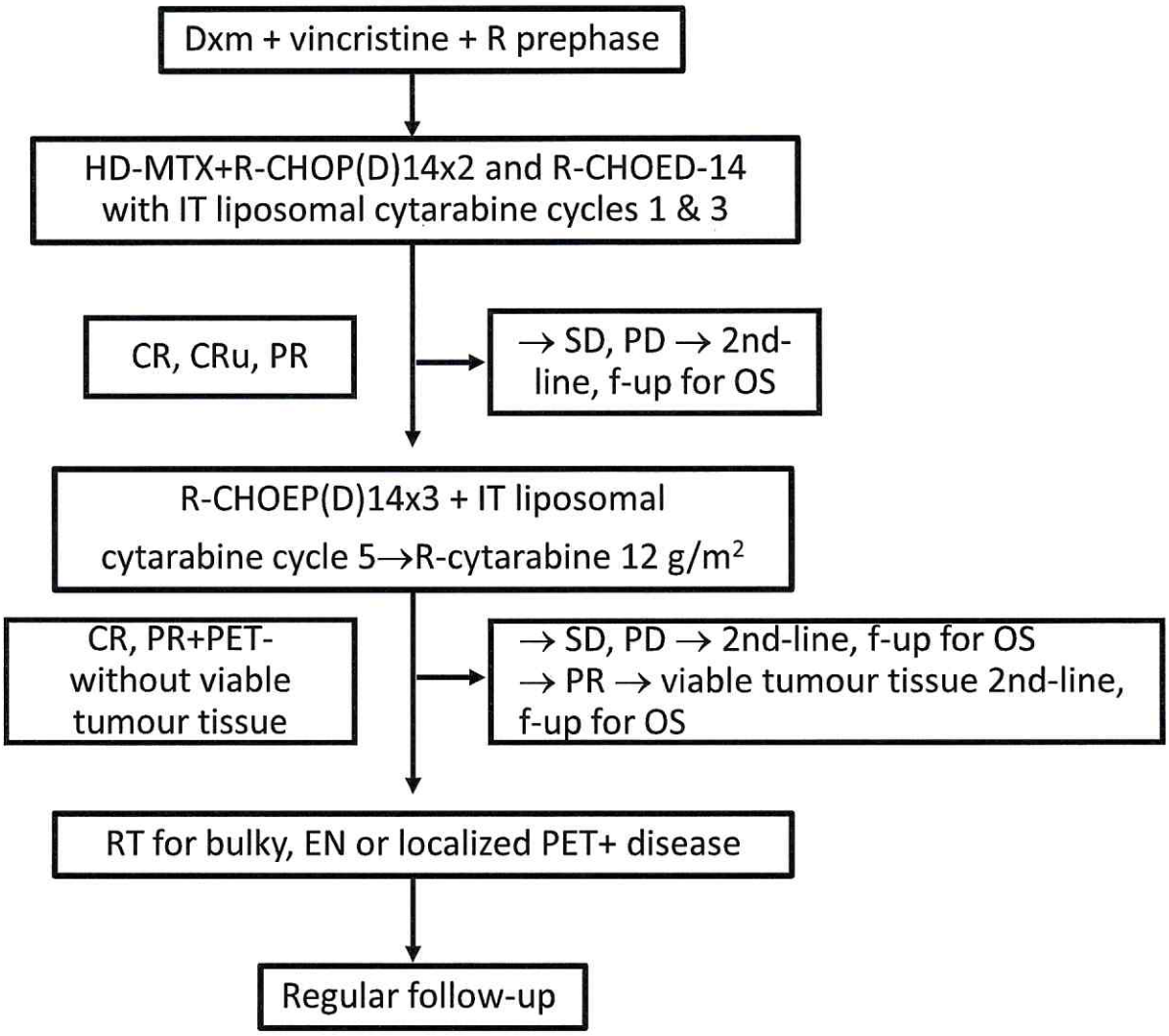
GCB, germinal centre B; TCRB, T-cell rich B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; FL, follicular lymphoma; PS, performance status; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dedydrogenase; aaIPI, age adjusted International Prognostic Index, CNS, central nervous system; CSF, cerebrospinal fluid

Table 2. Feasibility and toxicity

Adverse event (grades >2)	**n**	**%**
Grade 4 infection	16	12
Grade 3-4 mucositis	28	20
Grade 3 arachnoiditis	2	1.4
Grade 3-4 gastrointestinal toxicity	28	20
AML/MDS	4	3·1
PML	1	0·7
Treatment failure due to acute toxicity	9	6·5
Gastrointestinal hemorrhage	1	
Multiorgan failure	1	
Septicemia	2	
Unspecified toxicity	4	
Subdural hematoma	1	
Treatment related death	5	3·6
Gastrointestinal hemorrhage	1	
Multiorgan failure	1	
PML*	1	
Endocarditis**	1	
Toxicity unspecified	1	

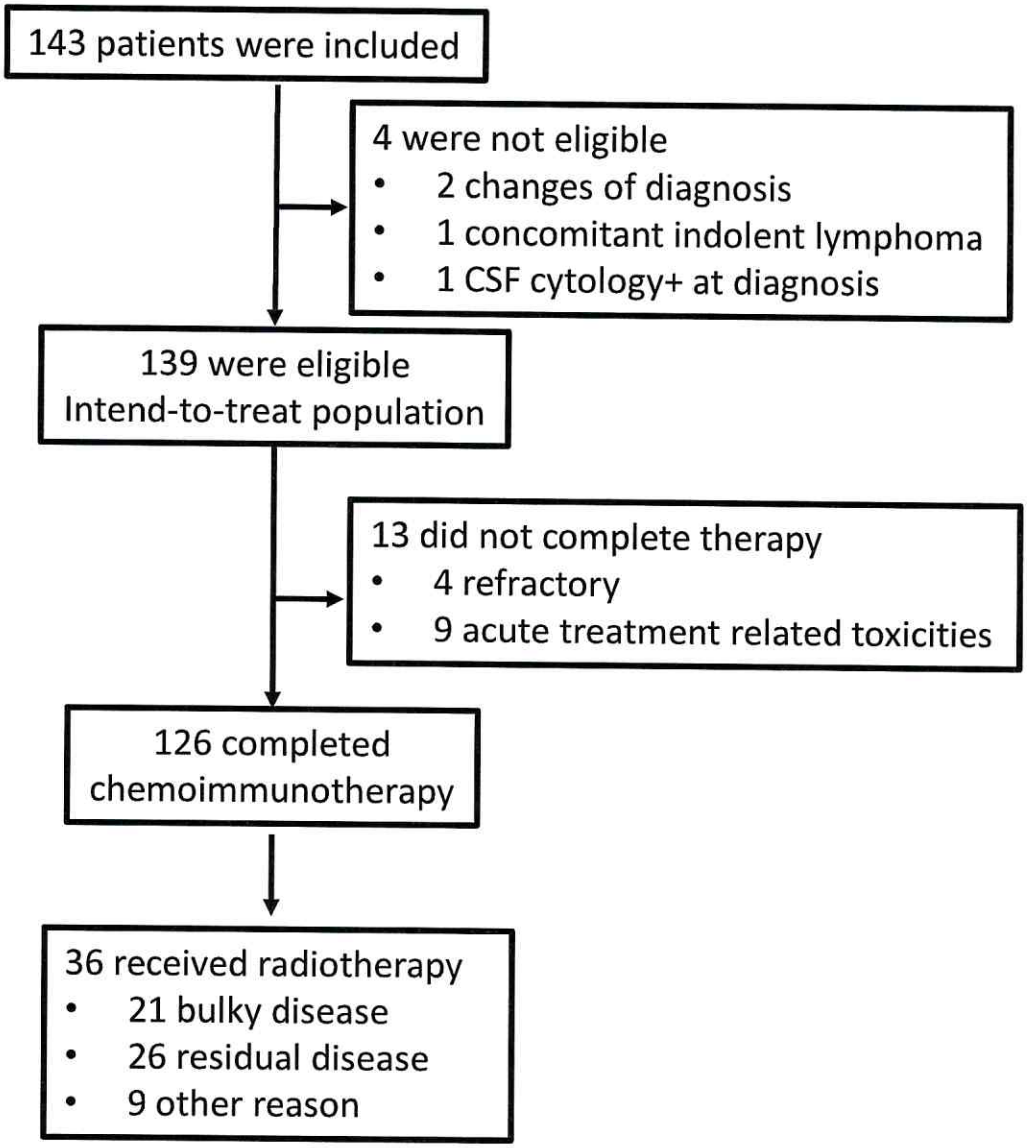
*First CR; **After relapse

Figure 1A



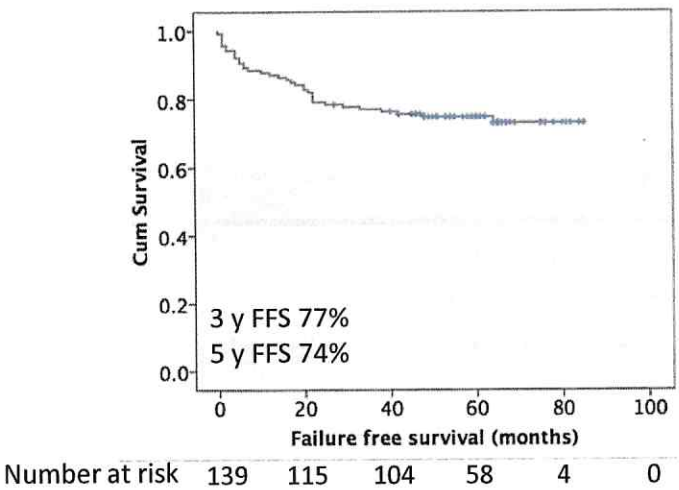
Leppä et al., Figure 1A

Figure 1B

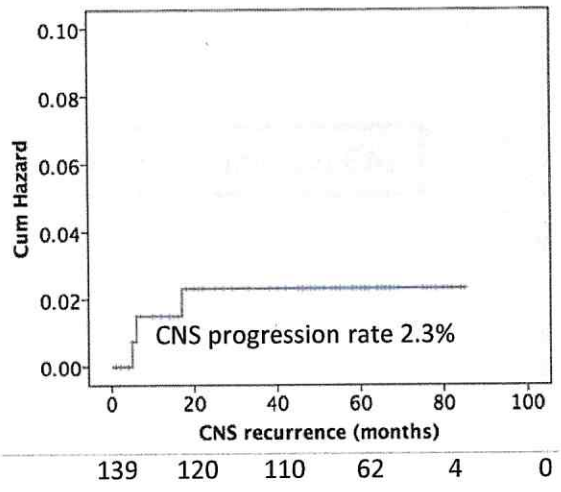


Leppä et al., Figure 1B

Figure 2



Number at risk 139 115 104 58 4 0



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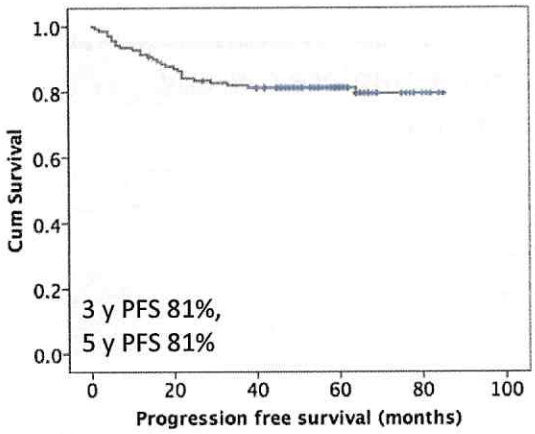

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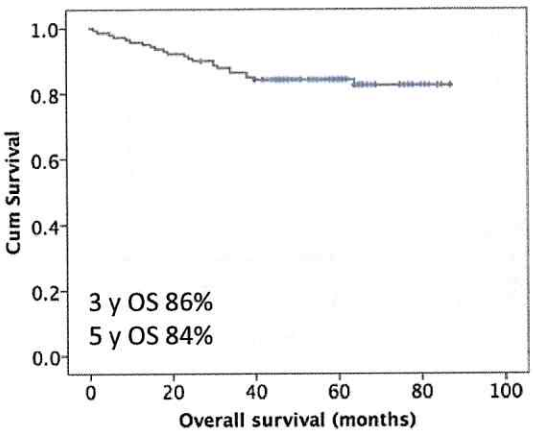
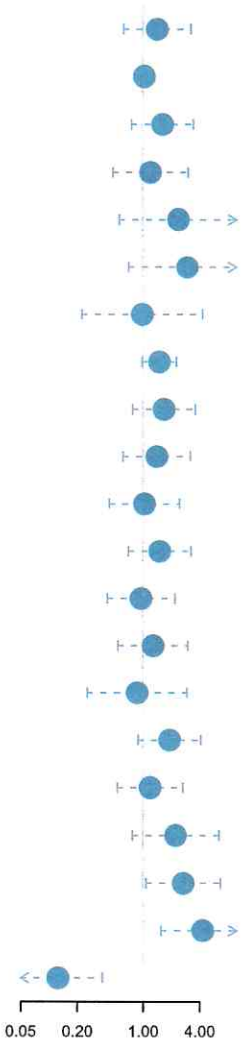


139 128 116 64 5 0

Leppä et al., Figure 2

Figure 3

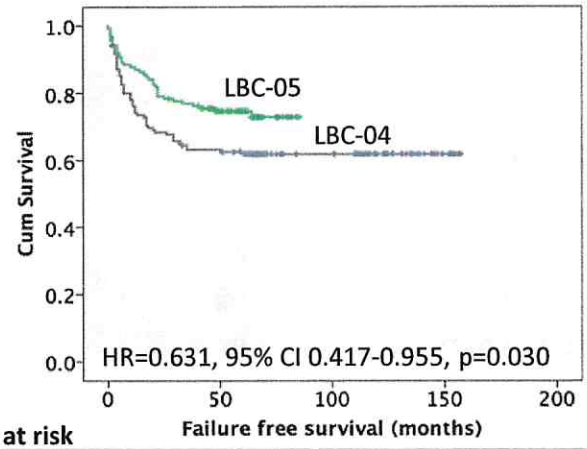
PFS	n (%)	HR (95% CI)	p−value
Male	88/139 (63)	1.436 (0.628−3.284)	0.391
Age (cont)	139/139 (100)	1.051 (1.003−1.101)	0.038
Age ≥ 60 y	47/139 (34)	1.637 (0.766−3.498)	0.203
nonGCB (vs GCB)	47/103 (42)	1.221 (0.485−3.077)	0.672
BCL2+	96/117 (82)	2.429 (0.567−10.398)	0.232
DPE	15/38 (40)	3.002 (0.716−12.579)	0.133
DHL	9/77 (12)	0.995 (0.227−4.350)	0.994
ECOG (cont)	139/139 (100)	1.507 (0.988−2.299)	0.057
ECOG PS > 1	43/139 (31)	1.692 (0.785−3.649)	0.180
B−symptoms	88/139 (63)	1.420 (0.622−3.246)	0.405
Stage IV	102/139 (73)	1.047 (0.443−2.476)	0.917
aaIPI 3	46/139 (33)	1.528 (0.708−3.294)	0.280
>1 EN sites	81/121 (67)	0.967 (0.423−2.209)	0.936
>2 EN sites	51/121 (42)	1.292 (0.549−3.044)	0.557
>3 EN sites	20/121 (17)	0.878 (0.259−2.981)	0.835
CNS−IPI high	63/139 (45)	1.940 (0.900−4.182)	0.091
Bulky disease	52/139 (37)	1.197 (0.537−2.666)	0.661
CSF flow +	11/139 (8)	2.235 (0.773−6.464)	0.138
DS 4−5	28/119 (24)	2.703 (1.086−6.724)	0.032
DS 5	12/119 (10)	4.356 (1.566−12.114)	0.005
Mtx ≥ 3 g/m2	133/139 (96)	0.126 (0.042−0.372)	0.003



Leppä et al., Figure 3

Figure 4

A



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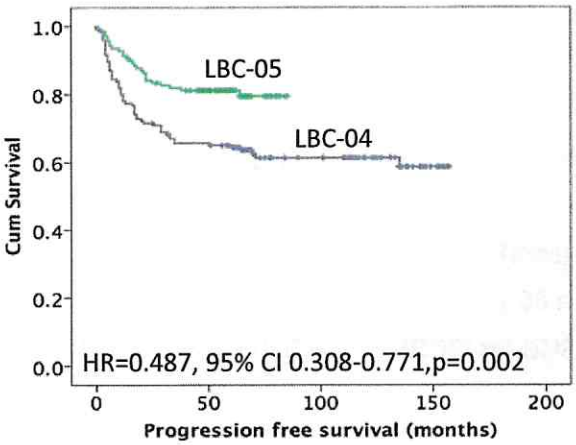
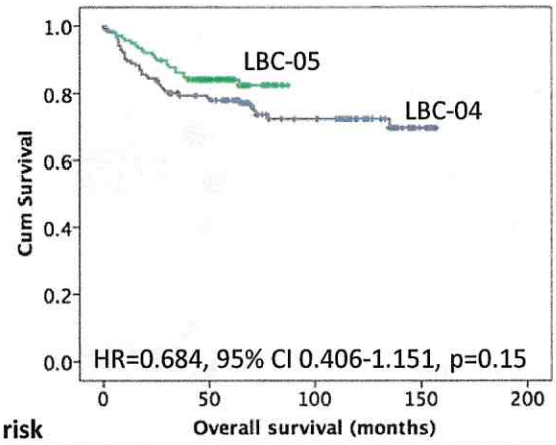


Number at risk										
LBC-05	139	81	0	0	0	139	87	0	0	0
LBC-04	156	95	45	7	0	156	99	46	7	0

C



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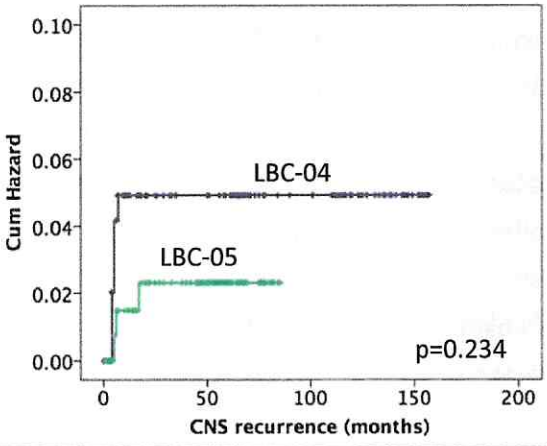
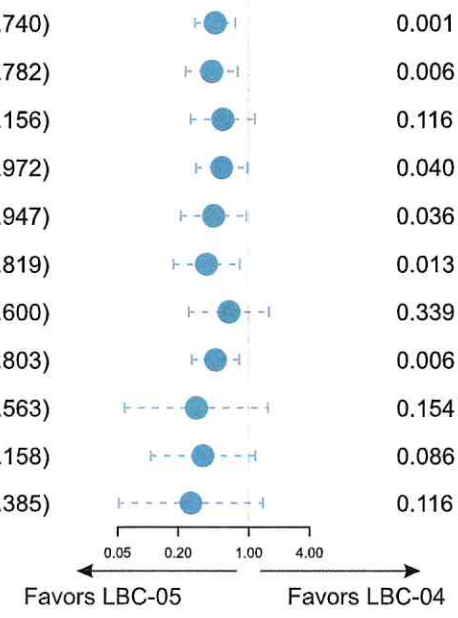


Number at risk										
LBC-05	139	90	0	0	0	139	89	0	0	0
LBC-04	156	111	54	9	0	156	99	46	7	0

E

PFS	All (n)	LBC−04	LBC−05	HR (95% CI)	p−value
All	295	156	139	0.467 (0.294−0.740)	0.001
Age < 60 y	207	115	92	0.431 (0.238−0.782)	0.006
Age ≥ 60 y	88	41	47	0.555 (0.267−1.156)	0.116
aaIPI2	200	117	83	0.542 (0.302−0.972)	0.040
aaIPI3	85	39	46	0.449 (0.213−0.947)	0.036
GCB	127	71	56	0.384 (0.180−0.819)	0.013
non−GCB	79	32	47	0.639 (0.255−1.600)	0.339
BCL2+	194	98	96	0.469 (0.273−0.803)	0.006
BCL2−	39	18	21	0.303 (0.059−1.563)	0.154
DPE	22	7	15	0.351 (0.107−1.158)	0.086
DHL	17	8	9	0.267 (0.051−1.385)	0.116



Leppä et al., Figure 4.

Supplementary Material

Click here to download Necessary Additional Data: Lepp et al Supplemental data.pdf

Study protocol

Click here to download Necessary Additional Data: CHIC protocol version 6 160913final.pdf