Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: a retrospective population-based study from the Nordic Lymphoma Group.

Wästerlid, Tove; Brown, P N; Hagberg, Oskar; Hagberg, H; Pedersen, L M; D'Amore, F; Jerkeman, Mats

Published in:
Annals of Oncology

DOI:
10.1093/annonc/mdt058

2013

Original Article

Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: A retrospective population-based study from the Nordic Lymphoma Group

T. Wästerlid[1], P. Brown[2], O. Hagberg[3], H. Hagberg[4], L.M. Pedersen[5], F. D'Amore[6], M. Jerkeman[1]

[1]Department of Oncology, Skåne University Hospital, Lund, Sweden, [2]Department of Haematology, Rigshospitalet, Copenhagen, Denmark, [3]Department of Tumour Epidemiology, Skåne University Hospital, Lund, Sweden, [4]Department of Oncology, Akademiska University Hospital, Uppsala, Sweden, [5]Department of Haematology, Roskilde Hospital, Roskilde, Denmark, [6]Department of Haematology, Århus University Hospital, Århus, Denmark

Corresponding author

Dr. M. Jerkeman

Department of Oncology

Skåne University Hospital

Lasarettsgatan 23

Lund SE-221 85

SWEDEN

Phone: +4646177520

Fax: +4646176080

Email: mats.jerkeman@med.lu.se

Abstract

Background: Standard treatment of adult Burkitt lymphoma is not defined due to the lack of randomized trials. In this situation, population-based data may represent a useful contribution in order to identify an optimal treatment strategy.

Patients and methods: The aims of this study were to investigate the outcome for adult HIV-negative BL with different chemotherapy regimens, and to assess possible improvement within the time frame of the study. The study population was identified through the Swedish and Danish lymphoma registries 2000-2009.

Results: A total of 258 patients were identified. Since 2000, overall survival (OS) improved significantly only for younger patients (<65 years). Intensive regimens such as the Berlin-Frankfurt-Münster, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) and cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide and cytarabine (CODOX-M/IVAC) were associated with a favourable 2 year OS of 82%, 83% and 69%, respectively. The low-intensive CHOP/CHOEP regimens achieved a 2 year OS of 38.8%, confirming their inadequacy for the treatment of BL. In a multivariate analysis, rituximab was not significantly associated with improved OS.

Conclusions: In this population-based retrospective series of adult BL, intensive chemotherapy regimens were associated with favourable outcome. The impact of the addition of rituximab remains uncertain and warrants further investigation.

Key words: Burkitt lymphoma, chemotherapy regimen, rituximab

Introduction

Burkitt lymphoma (BL) is a rare and highly aggressive lymphoid neoplasm derived from germinal centre B-cells. It accounts for approximately 1-2% of adult lymphomas in Western countries, and a total of 20-25 cases are seen in Sweden and Denmark (cumulative population: 25 mio) every year. The genetic hallmark of BL is the *MYC* translocation, which induces a highly proliferative state within the cells carrying the translocation[1]. There are three main subtypes of BL: sporadic, endemic and HIV-associated. The endemic variety is associated with Epstein Barr virus and malaria, and affects children in the equatorial region, whereas the sporadic subtype is the most frequently occurring in Western countries. A recent study of the Swedish Lymphoma Registry (SLR) confirmed advanced age, poor WHO performance status (PS) and elevated serum lactate dehydrogenase (S-LDH) as significant prognostic factors for adult BL [2].

Due to the rapid tumour growth, a prompt diagnosis and start of appropriate treatment are crucial in order to optimize outcome in BL [3]. The optimal standard treatment for adult BL is not yet entirely defined due to the rarity of the disorder and the consequent lack of prospective randomized trials. Hence, adults diagnosed with BL are exposed to a range of different chemotherapy regimens, according to a variety of different local therapeutic guidelines [4]. This may in turn result in variable outcomes. An evidence-based standardised treatment protocol for adult BL would therefore be highly desirable.

A number of studies have shown that adapted paediatric protocols consisting of multiple agents given within short and intensive schedules, including fractionated alkylating agents and CNS-prophylaxis with high-dose methotrexate with or without high-dose cytarabine, are effective also in the adult BL population, with long-term survival rates up to 90% [3, 5-10]. Most of these paediatric protocols were introduced among the treatment options of adult sporadic BL in the beginning of the 1990s [11]. However, due to advanced age or co-morbidity, a substantial number of patients do not

tolerate intensive therapy and end up receiving less intensive regimens , such as cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) [12, 13]. This is particularly unfavourable, since elderly patients also tend to present more often with disseminated disease [3].

The most frequently used regimens based on paediatric protocols are CODOX-M/IVAC (cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide and cytarabine), the German BFM (Berlin-Frankfurt-Munster, vincristine, ifosfamide, methotrexate, cytarabine, etoposide, cyclophosphamide, doxorubicin, betamethasone), and the French Lymphome Malins B (LMB) regimens. These have all shown rates of overall survival (OS) among adult BL patients similar to those achieved in the paediatric setting [7, 14-16]. The BFM regimen, as modified by the German Adult Acute Lymphoblastic Leukaemia (GMALL) group, demonstrated a 2-year OS of 82% in HIV negative BL patients [17]. The CODOX-M/IVAC regimen has been reported to be associated with 2-year OS-rates of 64-82% [3, 18]. In general, reported data indicate that intensive regimens are substantially more effective than CHOP in adult sporadic BL [6, 11, 13]. Other regimens used for BL include the Cancer and Leukemia Group B (CALGB) 9251 regimen [19], and the dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (DA-EPOCH) [20].

For several other B-cell lymphoma subtypes, addition of the anti-CD20 monoclonal antibody rituximab to chemotherapy has been shown to improve outcome. A few studies have reported a positive effect of rituximab given in combination with hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (Hyper CVAD) in patients with adult sporadic BL [21, 22]. Similar observations were reported for the combination of rituximab with CODOX-M/IVAC [23-25]. In Sweden and Denmark, the same protocols have been utilized since 2000 except for Hyper-CVAD, which was introduced in Sweden in 2005. Rituximab has been increasingly adopted for the treatment of in CD20-positive malignancies in this region since 2003-2004.

The aims of the present study were to determine the efficacy of different chemotherapy regimens in a population based series of adult BL patients in Sweden and Denmark, including the impact of rituximab addition, and to evaluate whether outcome has improved within the study observation

period (2000-2009).

Patients and methods

This is a collaborative study within the Nordic Lymphoma Group framework, based on collaboration between the Swedish and Danish Lymphoma Groups and their respective population-based registries. As previously described, the Swedish Lymphoma Registry (SLR) was established in 2000 by the Swedish Lymphoma Group, to expand the data already included in the Swedish Cancer Registry [26]. Data from the SLR are presented in annual reports (www.swedishlymphoma.se) and cover approximately 95-97% of all lymphoma cases diagnosed in Sweden.

As previously reported the lymphoma registry of the Danish Lymphoma Group was initiated in 1983 covering western Denmark (Jutland and Funen) and was extended in 1999 to include all patients with lymphoma in Denmark. It also issues annual reports (www.lymphoma.dk) and coverage is cross-checked against the Central Danish Cancer Registry as well as the Danish Central Registry of Pathology [27].

The study population in the present series includes all adult patients diagnosed with BL from January 1, 2000 through December 31, 2009 in Sweden and Denmark. Since 2007 detailed data on treatment have been added to the SLR. To collect data on treatment for Swedish patients added to the registry before 2007, a retrospective review of medical records was performed. Detailed data on response and relapse was not available for all patients.

The national pathology guidelines for BL diagnosis according to which the BL-patient cohort in this series has been diagnosed include the following criteria: a diffuse infiltrate of medium-sized cells of B-cell germinal centre immunophenotype, negative for terminal deoxynucleotidyl transferase (TdT) and with >95% expression of Ki-67, with or without demonstrable *MYC* aberration.

The following variables were analysed: date of diagnosis, sex, age, S-LDH, WHO PS, Ann Arbor stage, B-symptoms, bulky disease (>10 cm), extranodal presentation, year of diagnosis, 1st line

chemotherapy regimen, immunotherapy, and survival status. Rituximab was given once every treatment cycle in the BFM protocol and with CHOP/CHOEP, twice per cycle CODOX-M/IVAC, and twice during the first four cycles of Hyper-CVAD. Treatment with CODOX-M/IVAC and BFM was stratified according to risk group according to the orginal protocols. Data regarding survival status was collected from the respective national population registries.

Statistical methods

For estimation of OS rates, the Kaplan-Meier method was used. When comparing survival curves the log-rank test was utilized. Hazard ratios (HR) for the various variables were calculated at both univariate and multivariate level by Cox regression analysis. For frequency tabulation of e.g. clinico-pathological features, prognostic factors and treatment regimens, the Pearson chi-square and non-parametric tests were utilised. All *p*-values were two-sided and values were regarded statistically significant if $p<0.05$. All statistical calculations were performed with SPSS version 20.

Results

Patient characteristics

A total of 258 patients were diagnosed between January 1, 2000 and December 31, 2009. Of these, a total of 122 (47 %) patients died. The median follow-up for surviving patients was 58 months. The median age was 56 years (range: 15-93 years). There was a male to female ratio of 2.6:1. The study cohort consisted of 90 (35 %) Danish and 168 (65 %) Swedish patients. Data on treatment was available for 205 (80 %) patients. Patient characteristics are summarised in Table 1.

Prognostic factors

As shown in Table 1, high age was the only parameter associated with impaired OS at both univariate and multivariate level. When stratifying into three age groups: <40 years, 40-65 years and

>65 years, the estimated two-year OS in the three groups was 86%, 65% and 23%, respectively. Poor performance status, elevated S-LDH, presence of B-symptoms, and bone marrow involvement were all associated with inferior survival at univariate level, but did not retain prognostic value in the multivariate analysis. CNS involvement, in all cases leptomeningeal, was not significantly associated with outcome. Gender, Ann Arbor stage, number of extranodal sites and the presence of bulky disease (>10 cm) had no significant prognostic impact (data not shown).

Chemotherapy regimens

Treatment-related data were available in 205 patients (79.5%). The distribution of chemotherapy regimens overall and among specific patient subsets is summarized in Table 2. Consecutive versions (1990/1995/2004) of the BFM regimen were the most commonly used treatment schedules in this series (34.6%). There was a significant age difference among patients receiving the various chemotherapy regimens. As expected, more intensive regimens (e.g. BFM, CODOX M/IVAC) were more frequently applied to younger patients and less intensive ones (CHOP, CHOEP) to elderly patients. Furthermore, patients receiving CHOP/CHOEP or no treatment more frequently presented with WHO PS>1 and elevated S-LDH. No difference in the presence of these factors was seen among the other regimens. All regimens were evenly distributed during the 2000-2009 time period, except for Hyper-CVAD, which was introduced in 2005. For 53 patients, treatment data were missing. The majority (33) were diagnosed in the earlier time period, 2000-2004. There was no difference in the distribution of prognostic factors in this group compared to that with complete treatment data. The Hyper-CVAD regimen was solely administered in Sweden, whereas the use of CODOX-M/IVAC was restricted to some Danish centres during the period covered by this study.

Overall survival

2-year OS estimates related to prognostic factors and chemotherapy regimens are shown in Table 2

and Figure 1. The high-intensive regimens BFM, Hyper-CVAD and CODOX-M/IVAC were all significantly superior to the low-intensive CHOP/CHOEP regimen after correcting for age and use of rituximab (HR=2.0 95% C. I.:1.0-4.1, *p*=0.04). To enable us to detect a potential difference in efficacy among the BFM, Hyper-CVAD and CODOX-M/IVAC regimens, an additional multivariate analysis was performed restricted for patients receiving these regimens, correcting for age and rituximab, but no significant difference between the individual regimens could be detected (Table 3). Patients presenting with CNS involvement obtained a 2-year overall survival of 45% . There was no indication of better outcome in patients receiving rituximab in this subgroup, but patients receiving intensive chemotherapy (BFM, CODOX-M/IVAC, Hyper-CVAD) had a significantly superior overall survival (p=0.05)

Improvement over time

In order to study whether outcome among patients with BL has improved since 2000, the study population was stratified into two groups according to year of diagnosis: 2000-2004 and 2005-2009. The 2-year OS rate for those diagnosed 2000-2004 was 52.6% compared to 61.3% among those diagnosed later. This difference was not statistically significant at multivariate level (HR=0.6, 95% C. I.: 0.2-1.4, *p*=0.2) for the study population as a whole. However, when stratifying the study population into patients up to 65 years or above 65 years, a statistically significant secular improvement in OS was found for the younger age group (2000-2004: 2-year OS 64.1%; 2005-2009: 79.4%; HR=0.5, 95% C. I.: 0.3-0.9, *p*=0.02). Corresponding 2-year OS rates for patients aged >65 were 21.7% and 22.9%, respectively (Figure 2). The distribution of prognostic factors was similar among patients diagnosed in the two time periods, in patients below and above 65 years, short of elevated LDH, which was more frequent among cases from the earlier time period. The median age among patients treated with CHOP/CHOEP was higher in the later time period (2000-2004: 65 years; 2005-2009: 70 years). In addition, patients receiving CHOP/CHOEP during 2005-2009 presented more frequently with a poor pre-therapeutic PS. In patients receiving intensive regimens, there were more

patients presenting with poor performance status (>1) in the earlier time period (38%), compared to 18% in the later period (p=0.01). For patients with missing treatment data, there was no difference in survival between the two time periods, 2-year OS 35.6% vs. 40.0%.

Rituximab

Information regarding the use of rituximab was available for 163 out of the 205 patients for whom chemotherapy data was available. Of the 163 patients, 111 (68%) received rituximab and 52 (32%) did not. Rituximab was mainly used from 2005 and onwards. In the univariate analysis, the addition of rituximab was associated with improved OS (HR=0.57, 95% C. I.:0.34-0.94, *p*=0.03). When stratifying the study population into three age groups, the favourable effect of rituximab on outcome was restricted to the cohort aged 40-65 (HR=0.46, 95% C.I.:0.21-0.98, *p*=0.047). However, when adjusting for age and chemotherapy regimen the addition of rituximab failed to sustain significance (Table 1). The improvement in 2-year OS when adding rituximab varied as follows among the chemotherapy regimens: 83.7%/81.8% for BFM with/without rituximab, 71.4%/66.7% for CODOX-M/IVAC with/without rituximab, 35%/33.3% for CHOP/CHOEP with/without rituximab. All patients treated with Hyper-CVAD received rituximab. There was no significant effect of rituximab addition in the univariate analysis when examining the various regimens individually.

Discussion

It is of importance to establish an effective standard treatment for adult BL, due to the aggressive nature of this disease and its high curability when properly treated. The two aims of this study were to evaluate and compare, in a population-based patient cohort, standard treatments for adult BL and to establish whether outcome among BL patients had improved over the 10-year time frame of this study (2000-2009). We found an improvement in OS over the observation period of this study among younger patients (up to 65 years), but not among elderly ones (>65 years). The median age of

our study population was 56 years, higher than previously reported [7, 12], which likely reflects the population based nature of the cohort. In terms of outcome prediction, advanced age was the only prognostic factor that retained independent prognostic value at both uni- and multivariate level. Surprisingly, CNS involvement did not prove a significant indicator of prognosis and 45% of patients exhibiting CNS involvement in this study were found to survive long-term, indicating that the CNS directed drugs, i e high dose methotrexate and cytarabine, incorporated in the high-intensive chemotherapy regimens are sufficient to eradicate CNS disease.

As expected, patients who received no treatment exhibited a very short survival time (<1 year). Their median age was 81 years, and they also more often presented with poor PS and elevated LDH. The low-intensive CHOP/CHOEP regimens achieved a 2-year OS of 38.8%, confirming that CHOP or CHOP-like regimens are inadequate for the treatment of BL [3]. Surprisingly, OS was better for patients treated with CHOP/CHOEP in the period 2000-2004 compared to those treated with the same regimen in the later 5-year period (2005-2009). This is likely to reflect a higher median age and a higher frequency of patients with poor PS in the latter group, indicating that more patients today receive high-intensive regimens. The outcome advances achieved within the last decade appear to have primarily benefited the younger and middle aged patient population. This highlights the need to develop regimens especially suited for patients of advanced age, such as the DA-EPOCH-R [28] and the modified B-ALL/NHL2002 [17] schedules. The 2-year OS of patients who received CODOX-M/IVAC was estimated at 69% in this series. The CODOX-M/IVAC (Magrath) regimen is widely used globally and has been studied in a number of retrospective studies, with similar outcome in terms of OS as in our study [14, 23-25]. The pattern of survival after CODOX-M/IVAC regimen was somewhat different than for BFM and Hyper-CVAD since 4 of 27 patients alive one year after diagnosis subsequently developed relapse and died, 3 of the 4 without rituximab initially. As this relapse pattern is unusual with BL, it cannot be ruled out that these patients may have been misdiagnosed. In this series, the BFM and Hyper-CVAD regimens were associated with the highest 2-year OS rates, 82% and 83% respectively.

Whether the addition of rituximab to the treatment regimens contributed to the OS improvement observed in younger patients (≤65) during the later time period, cannot be conclusively clarified by the present retrospective study. Rituximab was associated with a statistically significant improvement in OS at univariate level. However, this significance disappeared when correcting for age and use of chemotherapy regimen. In addition, missing information of treatment and rituximab was mainly present in the earlier time-period and this may also contribute to lack of significance in the multivariate analysis. OS was only marginally improved by the addition of the antibody in patients who received BFM or CHOP/CHOEP. For patients treated with CODOX-M/IVAC the improvement was more evident, although not statistically significant, in line with recent retrospective series [23-25], as well as one prospective report [29], where the addition of rituximab to CODOX-M/IVAC was found to improve OS compared with historical controls. Similarly, a number of retrospective trials have evaluated the effect of adding rituximab to Hyper-CVAD and have found it beneficial compared to Hyper-CVAD alone [11, 21, 22]. In the present series, all patients treated with Hyper-CVAD had also received rituximab, precluding us from making this comparison. In patients treated with BFM, similar two-year OS rates of over 80% were achieved irrespectively of rituximab addition. Thus, the effect of rituximab addition in BL treatment cannot be determined in this study, and the potential impact of this agent in BL treatment warrants further investigation.

A limitation in a population based study, such as this, is the lack of central pathology review. This study is likely to contain cases that would not be classified as true BL cases according to the current WHO criteria even though uniform diagnostic criteria have been applied. Particularly in the cohort aged over 40 years a proportion of patients included in this study would now likely be classified as B-cell lymphoma intermediate between BL and DLBCL. However, there are data suggesting that patients diagnosed with lymphomas with such characteristics may benefit from the same short, high-intensive multiagent protocols as used when treating BL [23, 29].

In the absence of randomized trials, population-based data, such as those presented in this study, are among the few sources of evidence that can contribute to the establishment of rational

treatment recommendations for non HIV-associated adult BL. Based upon population-based data from Sweden and Denmark , we can conclude that patients with adult BL should optimally receive intensive chemotherapy regimens, and that outcome among younger adult BL patients (≤ 65 years) has improved over the last decade. However, novel treatment strategies are needed for elderly BL patients.

Disclosures

The authors have declared no conflicts of interest.

References

1. Dalla-Favera R, Bregni M, Erikson J et al. Human c-myc onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells. Proc Natl Acad Sci U S A 1982; 79: 7824-7827.
2. Wasterlid T, Jonsson B, Hagberg H, Jerkeman M. Population based study of prognostic factors and treatment in adult Burkitt lymphoma: a Swedish Lymphoma Registry study. Leuk Lymphoma 2011; 52: 2090-2096.
3. Kasamon YL, Swinnen LJ. Treatment advances in adult Burkitt lymphoma and leukemia. Curr Opin Oncol 2004; 16: 429-435.
4. Kelly JL, Toothaker SR, Ciminello L et al. Outcomes of patients with Burkitt lymphoma older than age 40 treated with intensive chemotherapeutic regimens. Clin Lymphoma Myeloma 2009; 9: 307-310.
5. Perkins AS, Friedberg JW. Burkitt lymphoma in adults. Hematology Am Soc Hematol Educ Program 2008; 341-348.
6. Divine M, Casassus P, Koscielny S et al. Burkitt lymphoma in adults: a prospective study of 72 patients treated with an adapted pediatric LMB protocol. Ann Oncol 2005; 16: 1928-1935.
7. Mead GM, Barrans SL, Qian W et al. A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). Blood 2008; 112: 2248-2260.
8. Thomas DA, Cortes J, O'Brien S et al. Hyper-CVAD program in Burkitt's-type adult acute lymphoblastic leukemia. J Clin Oncol 1999; 17: 2461-2470.
9. Magrath I, Adde M, Shad A et al. Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. J Clin Oncol 1996; 14: 925-934.
10. Philip T, Meckenstock R, Deconnick E et al. Treatment of poor prognosis Burkitt's lymphoma in adults with the Societe Francaise d'Oncologie Pediatrique LMB Protocol--a study of the Federation Nationale des Centres de Lutte Contre le Cancer (FNLCC). Eur J Cancer 1992; 28A: 1954-1959.
11. Linch DC. Burkitt lymphoma in adults. Br J Haematol 2011.
12. Blum KA, Lozanski G, Byrd JC. Adult Burkitt leukemia and lymphoma. Blood 2004; 104: 3009-3020.
13. Smeland S, Blystad AK, Kvaloy SO et al. Treatment of Burkitt's/Burkitt-like lymphoma in adolescents and adults: a 20-year experience from the Norwegian Radium Hospital with the use of three successive regimens. Ann Oncol 2004; 15: 1072-1078.
14. Lacasce A, Howard O, Lib S et al. Modified magrath regimens for adults with Burkitt and Burkitt-like lymphomas: preserved efficacy with decreased toxicity. Leuk Lymphoma 2004; 45: 761-767.
15. Reiter A, Schrappe M, Tiemann M et al. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: A report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. Blood 1999; 94: 3294-3306.
16. Soussain C, Patte C, Ostronoff M et al. Small noncleaved cell lymphoma and leukemia in adults. A retrospective study of 65 adults treated with the LMB pediatric protocols. Blood 1995; 85: 664-674.
17. Oriol A, Ribera JM, Bergua J et al. High-dose chemotherapy and immunotherapy in adult Burkitt lymphoma: comparison of results in human immunodeficiency virus-infected and noninfected patients. Cancer 2008; 113: 117-125.
18. Di Nicola M, Carlo-Stella C, Mariotti J et al. High response rate and manageable toxicity with an intensive, short-term chemotherapy programme for Burkitt's lymphoma in adults. Br J Haematol 2004; 126: 815-820.

19. Lee EJ, Petroni GR, Schiffer CA et al. Brief-duration high-intensity chemotherapy for patients with small noncleaved-cell lymphoma or FAB L3 acute lymphocytic leukemia: results of cancer and leukemia group B study 9251. J Clin Oncol 2001; 19: 4014-4022.
20. Wilson WH, Grossbard ML, Pittaluga S et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood 2002; 99: 2685-2693.
21. Thomas DA, Faderl S, O'Brien S et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006; 106: 1569-1580.
22. Fayad L, Thomas D, Romaguera J. Update of the M. D. Anderson Cancer Center experience with hyper-CVAD and rituximab for the treatment of mantle cell and Burkitt-type lymphomas. Clin Lymphoma Myeloma 2007; 8 Suppl 2: S57-62.
23. Maruyama D, Watanabe T, Maeshima AM et al. Modified cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M)/ifosfamide, etoposide, and cytarabine (IVAC) therapy with or without rituximab in Japanese adult patients with Burkitt lymphoma (BL) and B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and BL. Int J Hematol 2010; 92: 732-743.
24. Barnes JA, Lacasce AS, Feng Y et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Ann Oncol 2011; 22: 1859-1864.
25. Mohamedbhai SG, Sibson K, Marafioti T et al. Rituximab in combination with CODOX-M/IVAC: a retrospective analysis of 23 cases of non-HIV related B-cell non-Hodgkin lymphoma with proliferation index >95%. Br J Haematol 2011; 152: 175-181.
26. Abrahamsson A, Dahle N, Jerkeman M. Marked improvement of overall survival in mantle cell lymphoma: a population based study from the Swedish Lymphoma Registry. Leuk Lymphoma 2011; 52: 1929-1935.
27. Gang AO, Strom C, Pedersen M et al. R-CHOEP-14 improves overall survival in young high-risk patients with diffuse large B-cell lymphoma compared with R-CHOP-14. A population-based investigation from the Danish Lymphoma Group. Ann Oncol 2011.
28. Wilson WH, Dunleavy K, Pittaluga S et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. J Clin Oncol 2008; 26: 2717-2724.
29. Corazzelli G, Frigeri F, Russo F et al. RD-CODOX-M/IVAC with rituximab and intrathecal liposomal cytarabine in adult Burkitt lymphoma and 'unclassifiable' highly aggressive B-cell lymphoma. Br J Haematol 2012; 156: 234-244.

Table 1

Estimated two-year overall survival and hazard ratio for prognostic factors according to univariate and multivariate Cox Regression analysis

			Univariate analysis			Multivariate analysis		
Variable	*n* (%)	2-year overall survival	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age[a]								
Below 40	65 (25)	86.2%						
40-65	115 (45)	65.2%	>40: 4.6	2.5-8.6	*<0.01*			
Above 65	78 (30)	22.6%	>65: 4.5	3.1-6.4	*<0.01*	1.04	1.0-1.1	*<0.01*
WHO performance status								
0-1	163 (65)	72.6%						
2-4	89 (35)	32.4%	3.5	2.4-5.1	*<0.01*	1.9	0.9-3.9	*0.09*
LDH								
Normal	52 (22)	84.6%						
Elevated	188 (78)	52.0%	3.3	1.8-6.1	*<0.01*	1.7	0.7-4.3	*0.3*
Bone marrow								
involvement	91 (35)	49.4%	1.5	1.0-2.1	*0.03*	0.9	0.5-1.8	*0.8*
CNS involvement	22 (8.5)	45.5%	1.5	0.8-2.6	*0.2*	1.4	0.6-3.2	*0.5*
B-symptoms	141 (55)	50.3%	1.8	1.2-2.6	*<0.01*	1.6	0.8-3.6	*0.2*
Year								
2000-04	108 (42)	52.6%						
2005-09	150 (58)	61.3%	0.8	0.5-1.2	*0.3*	1.9	0.7-4.8	*0.2*
Rituximab								
No	52 (32)	55.8%						
Yes	111 (68)	70.3%	0.6	0.3-0.9	*0.03*	0.4	0.2-1.1	*0.07*
Chemotherapy regimen								

BFM[b]	71 (36)	81.7%	-	-	-	-	-	-
Hyper-CVAD	29 (15)	82.8%	1.0	0.4-2.7	*0.9*	1.2	0.3-4.2	*0.8*
CODOX/M-IVAC	32 (16)	68.6%	1.9	0.9-4.0	*0.1*	2.1	0.7-5.9	*0.2*
CHOP/CHOEP	49 (25)	38.8%	4.2	2.3-7.8	*<0.001*	2.4	0.8-7.2	*0.1*
Other	18 (9)	33.3%	5.2	2.5-10.8	*<0.001*	3.4	1.0-11	*0.04*

[a]In the multivariate analysis, age was analyzed as a continuous variable.

[b]Reference category.

Table 2

Distribution and two-year overall survival rates of chemotherapy regimens in relation to prognostic factors. Survival rates were compared with log rank tests, and p-values for comparisons are shown.

	BFM		Hyper-CVAD		CODOX-M/IVAC		CHOP/ CHOEP		Other		No treatment	
	71		29		32		49		18		6	
dian age (years)	40		56		42		66		67.5		81	
ear OS	81.7		82.8		68.6		38.8		33.3		0	
	N (%)	2-y OS (*p-value)*	*N* (%)	2-y OS (*p-value*)	*N* (%)	2-y OS (*p-value*)	*N* (%)	2-y OS (*p-value)*	*N* (%)	2-y OS (*p-value*)	*N* (%)	2-y OS (*p-value*
e												
elow 40	*35* (49.3)	94.3	*4* (13.8)	75.0	*13* (40.6)	76.9	*3* (6.1)	100	*1* (5.6)	-	*1* (16.7)	0
0-65	*34* (47.9)	73.5	*21* (72.4)	85.7	*18* (56.2)	66.7	*20* (40.8)	45	*6* (33.3)	50	*1* (16.7)	0
bove 65	*2* (2.8)	0	*4* (13.8)	75	*1* (3.1)	0	*26* (53.1)	26.9	*11* (61.1)	18.2	*4* (66.7)	0
		(*<0.01*)		(*0.8*)		(*0.2*)		(*0.06*)		(*0.2*)		(*0.5*)
HO PS												
-1	*51* (73.9)	88.2	*25* (89.3)	88.0	*20* (62.5)	75.0	*26* (55.3)	53.8	*11* (61.1)	45.5	*1* (16.7)	0
-4	*18* (26.1)	66.7	*3* (10.7)	33.3	*12* (37.5)	58.3	*21* (44.7)	19	*7* (38.9)	14.3	*5* (83.3)	0
		(*0.02)*		*(<0.01*)		(*0.4*)		(*<0.01*)		(*0.2*)		(*0.6*)
DH												
lormal	*24* (35.3)	91.7	*7* (24.1)	100	*6* (20.0)	83.3	*5* (10.6)	60	*5* (27.8)	60	*0* (0)	0
levated	*44* (64.7)	77.3	*22* (75.9)	77.3	*24* (80.0)	62.5	*42* (89.4)	38.1	*13* (72.2)	23.1	*5* (100)	0
		(*0.2)*		(*0.2)*		(*0.4)*		(*0.4)*		(*0.2)*		(-)
ne marrow olvement												
es	*24* (33.8)	79.2	*8* (27.6)	75.0	*15* (46.9)	53.3	*17* (34.7)	23.5	*9* (50.0)	33.3	*3* (50.0)	0
o	*47* (66.2)	83.0	*21* (72.4)	85.7	*17* (53.1)	82.4	*32* (65.3)	46.9	*9* (50.0)	33.3	*3* (50.0)	0
		(*0.7*)		(*0.5*)		(*0.1*)		(*0.1*)		(*0.9*)		(*0.6*)
S Involvement												
	6 (8.5)	66.7	*2* (6.9)	100	*2* (6.2)	50	*3* (6.1)	0	*4* (22.2)	25	*0* (0)	0
		83.1	*27* (93.1)	81.5	*30* (93.8)	69.8	*46* (93.9)	41.3	*14* (77.8)	35.7	*6* (100)	0
	65 (91.5)	(*0.2*)		(*0.5*)		(*0.6*)		(*0.5*)		(*0.6*)		(-)
ymptoms												
es	*34* (50.0)	82.4	*15* (53.6)	73.3	*20* (62.5)	55.0	*24* (51.1)	25.0	*12* (66.7)	16.7	*4* (66.7)	0
o	*34* (50.0)	85.3	*13* (46.4)	92.3	*12* (37.5)	91.7	*23* (48.9)	52.2	*6* (33.3)	66.7	*2* (33.3)	0
		(*0.7*)		(*0.2*)		(*0.04*)		(*0.1*)		(*0.1*)		(*0.5*)
ar												
000-04	*27* (38.0)	77.8	*0* (0)	-	*15* (46.9)	66.7	*24* (49)	45.8	*8* (44.4)	37.5	*1* (16.7)	0
005-09	*44* (62.0)	84.1	*29* (100)	82.8	*17* (53.1)	70.6	*25* (51)	32	*10* (55.6)	30	*5* (83.3)	0
		(*0.5*)		(-)		(*0.9*)		(*0.73*)		(*0.6*)		(*0.1*)
untry												
enmark	*17* (23.9)	82.4	*0* (0)	-	*32* (100)	68.6	*18* (36.7)	33.3	*10* (55.6)	20	*2* (33.3)	0
weden	*54* (76.1)	81.5	*29* (100)	82.8	*0* (0)	-	*31* (63.3)	41.9	*8* (44.4)	50	*4* (66.7)	0
		(*1.0*)		(-)		(-)		(*0.3*)		(*0.2*)		(*0.9*)
uximab												
es	*43* (60.5)	83.7	*28* (96.6)	85.7	*14* (43.8)	71.4	*15* (30.6)	35	*6* (33.3)	16.7	*0* (0)	0
lo	*11* (15.5)	81.8	*0* (0)	-	*18* (56.2)	66.7	*20* (40.8)	33.3	*8* (44.4)	37.5	*6* (100)	0
Missing	*17* (24.0)	76.5	*1* (3.4)	0	*0* (0)	-	*14* (28.6)	50	*4* (22.2)	50	*0* (0)	0
		(*0.9*)		(-)		(*0.8*)		(*0.8*)		(*0.4*)		(-)

Table 3

Multivariate analysis of overall survival with intensive chemotherapy regimens (BFM, Hyper-CVAD and CODOX/M-IVAC) adjusted for age, performance status and use of rituximab. The BFM regimen was used as the reference category

	Hazard Ratio (HR)	95% Confidence Interval for HR	*p*-value
Age[a]	1.038	1.017-1.060	*<0.01*
Rituximab	0.979	0.573-1.720	*0.98*
BFM	-	-	-
Hyper-CVAD	0.671	0.217-2.077	*0.49*
CODOX/M-IVAC	2.124	0.879-5.133	*0.24*

[a]Continuous variable

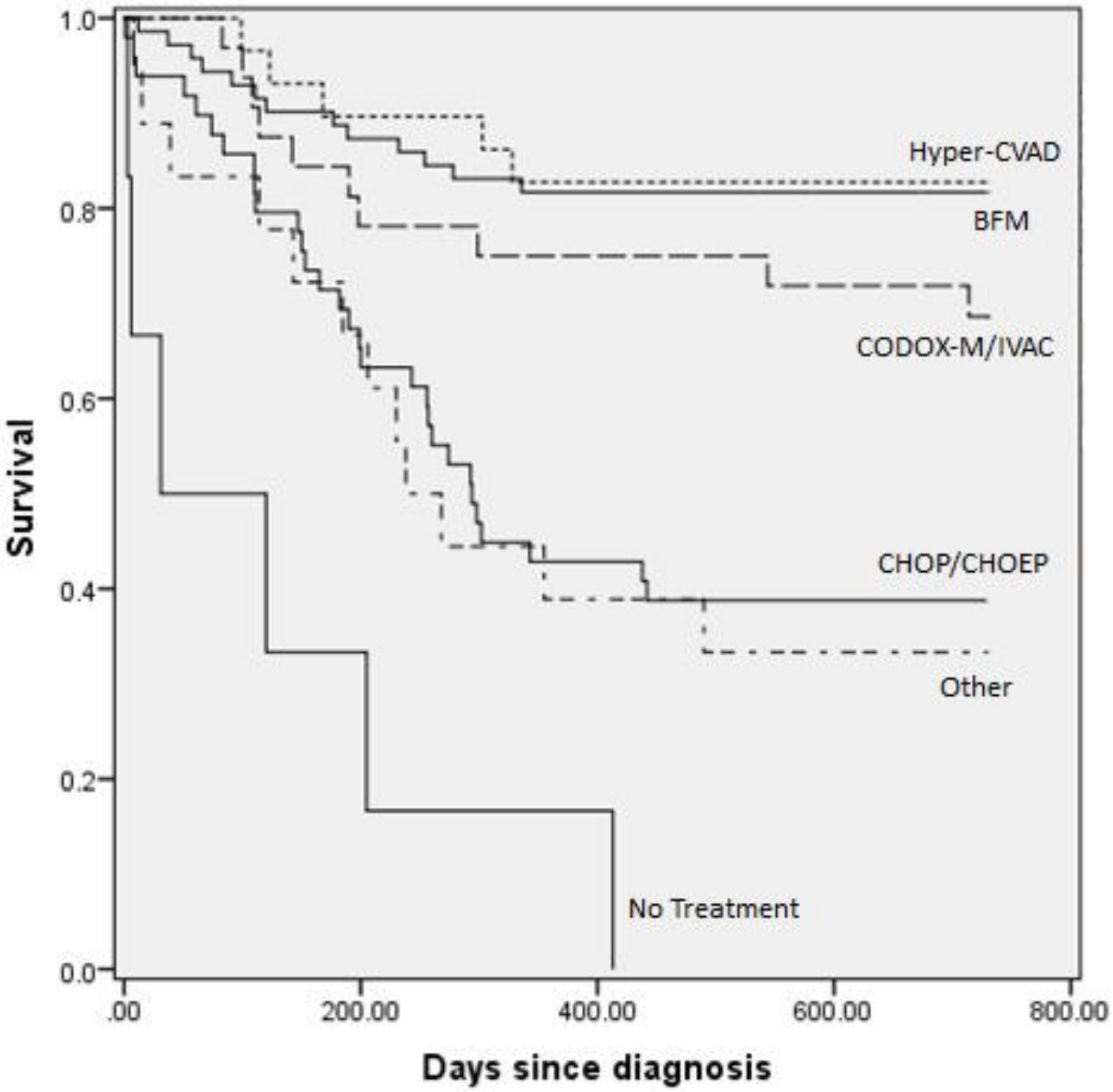
Figure legends

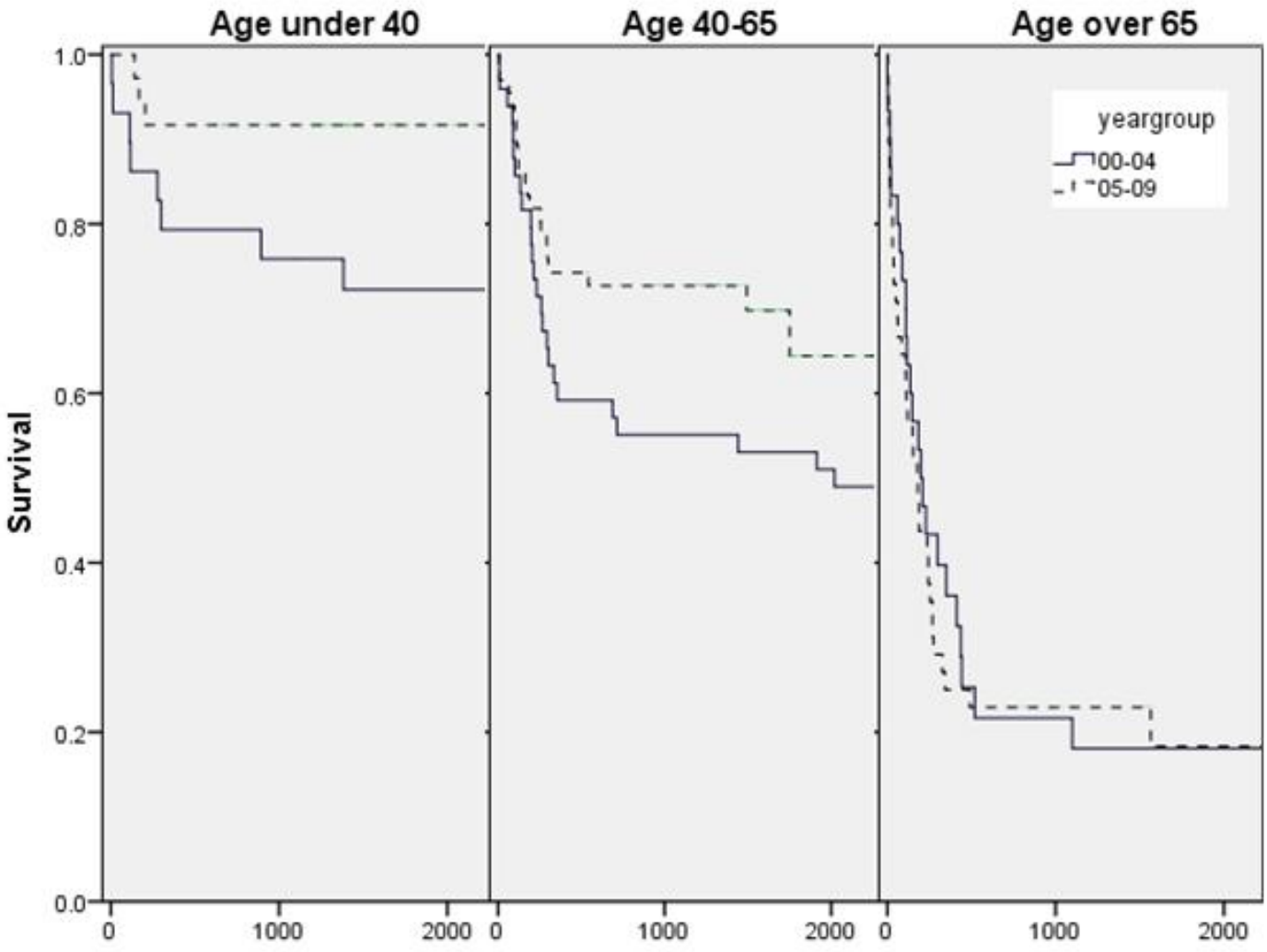
Figure 1

Overall survival according to chemotherapy regimen, with patients receiving/not receiving rituximab pooled.

Figure 2

Overall survival according to time of diagnosis, diagnosed 2000-2004 or 2005-2009 (broken line), in age groups <40 years, between 40-65 and >65 years


1.0
0.8
0.6
0.4
0.2
0.0
Survival
Hyper-CVAD
BFM
CODOX-M/IVAC
CHOP/CHOEP
Other
No Treatment
.00
200.00
400.00
600.00
800.00
Days since diagnosis


Age under 40
Age 40-65
Age over 65
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
yeargroup
00-04
05-09